

Tumor biomarkers from discovery to clinical practice

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Abstract

A tumor marker is a chemical that acts as a tumor indication. Tumor biomarkers are undefined in origin, but they indicate the existence of a certain tumor. The detection of a specific tumor is aided by an increase or decrease in the concentration of marker concentrations. Gene expression arrays, proteomic technologies, and high-throughput sequencing are some of the current methods for detecting cancer. This detection is important for treatment, prognosis, and determining the success of treatment. Tumor biomarkers are also used to monitor recurrence. Biomarkers are now being used extensively in medical research and drug development to combat tumors. Some people believe that tumor biomarkers are better for monitoring than for diagnosis.

Keywords: Tumor, Tumor biomarkers, Nature, Function, Classification

Introduction

Tumor Biomarkers are the substances secreted by a cancerous cell or other body cell to indicate the presence of cancer in the body [1]. These markers can be found in the tumor tissue, urine, blood, and stool of the cancer patients [2]. These markers are secreted both by a normal cell and a cancerous cell, but in normal cell, concentration of tumour markers is very low as compared to the cancerous cells. Its high concentration in the cancerous cell is an indicator of the presence of a specific type of cancer [3,4]. A range of different markers has been identified so far, some of them are linked with single type of cancer and some are linked with multiple types of cancer [5,6]. They are formed as a result of modifications in the genetic sequence, metabolites and in proteins expression [7,8].

Nature of biomarker is not defined, as some are protein in nature (receptor, enzyme), some are nucleic acid based including microRNA and non-coding RNA, whereas some are antibodies in nature [9,10]. Detailed classification of tumor biomarkers is shown in **Table 2**.

Some examples of tumor markers include, an inadequate concentration of Glutathione S-transferase P1 (GSTP1) marker which indicates the presence of prostate cancer [11], Short-stature homeobox 2 (*SHOX2*) indicates lungs cancer [12], breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) is the most common biomarkers in breast cancer and several others that are secreted in the presence of a certain type of cancer [13].

Today, biomarkers are seen as a crucial key to treat this disease [14]. A number of biomarker-based drugs are available that are used against this silent killing disease. Biomarker based therapies also enhance the effectiveness of cancer [15,16].

History of Tumor Biomarkers

History of tumor biomarkers was dated back to 1846 when a protein was found in the urine sample of myeloma cancer patient. Later, research on tumor biomarkers changed the way cancer was seen. Today, biomarker-based drugs are available and frequently used in cancer treatment. Timeline of tumor biomarker is shown in **Table 1** [17].

Then from 1975 till 2017, there are a lot of researchers that contribute in the research of tumor biomarker to eliminate this disease but at that time researchers neither used these markers for diagnosing nor for treatment purpose, they only identify them as a unique thing [17].

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Table1. Timeline of tumor biomarker.			
Name of observer	Year	Observation	
Bence Jones	1846	Observe protein in the urine that show only in myeloma	17
Brown	1928	Ectopic production of hormones by tumors	17
Zondek	1930	Human chorionic gonadotropin	17
Gushing	1932	Adrenocorticotrophic hormone	17
Gutman et al.	1933	Prostatic acid phosphatase in prostatic cancer	17
Markert	1959	Isoenzymes in tissue differentiation	17
	1960	Found in breast cancer	1
Newell	1960	Philadelphia Chromosome	17
Abelev	1963	Alpha-fetoprotein in liver carcinoma	17
Gold and Freedman	1965	Carcinoembryonic antigen in colon cancer	17
Huebner and Todaro	1969	Oncogenes as transforming factors	17
Kohler and Milstein	1975	Monoclonal production of antibodies of defined specificities	17
	1971-1980	Prostate specific antigen was detected in human	3
	1990	Brca1 & Brca2 responsible in breast or ovarian cancer	2
Ward and Billroth	1854	A tumor of bladder and other urinary tract named as inverted papilloma were discovered. In 2016 list of scientists found that collagen contribute to cancer progression.	4,5
Rigoni-stern	1842	Cervical cancer is noticed in married woman. Later on, Tumor virus protein have been identified and, presence of different Immune complex against virus act as a marker.	6
	1996	Brain tumor first noticed by Gupta in 1973, later found that Brain tumor is related to the low level of MGMT protein .	7,8
Hughes DJ, et al.	2016	Low level of selenium chemical in blood increases the risk of liver cancer	9
W. HANNA, et al.	1967	Renin is a potential biomarker in Juxtaglomerular cell tumor (a rare kidney tumor)	10
H Koprowski, et al.	1979	Biomarker named as CA 19-9 is associated with Pancreatic cancer	11,12
Enders KO Ng, et al.	2009	MicroRNA is reported as a biomarker in the screening of Colorectal Cancer	13

Nature of Tumor Biomarkers.

The nature of biomarkers is diverse, ranging from being protein to hormones, and antigens. Categorization of tumor biomarkers on the basis of their nature is shown in **Table 2**.

Function of Tumor Biomarkers

Tumor biomarkers play important functions before and after tumor development. They differ on the basis of their function, treatment, location, response to treatment. A short summary of the various aspects making biomarkers different from one another is given below.

Role of biomarker in normal cell as-well-as in cancer cell

Human epidermal growth factor receptor 2 (HER2) plays a crucial role in the normal development of a cell. Over-expression of these types of proteins serves as a tumor biomarker [43]. Because of over-expression, cells grow faster than the normal cells and may happen that this biomarker spread into other parts of the body. It is possible to stop the spread of these proteins by disrupting their

signalling pathway [44,45].

Role of tumor biomarkers in enhancing the effectiveness of treatment

Secreted Protein Acidic And Cysteine Rich (*SPARC*) encodes a protein which is acidic in nature and cysteine rich. The encoded protein mainly serves as a transporter of albumin into the cell. Albumin is used in some chemical based therapies to prevent dissolution in blood and to target specific cells. Over expressed *SPARC* serves as a biomarker and also enhances the effectiveness of the treatment [46,47].

Biomarker role in disruption treatments

Chemotherapeutic drugs are made with platinum to disturb tumor DNA [48]. ERCC1 is a protein which plays a role in repairing tumor DNA. High level of ERCC1 is used as a tumor biomarker and also indicates that the drug will not be able to damage the tumor DNA. Silencing of this gene for a while is also helpful to treat cancer [49,50].

Table 2. Categorization of tumor biomarkers on the basis of their nature.		
Tumor biomarker Nature	Name of biomarker	References
1. Protein	Beta ₂ -microglobulin, Prostate specific antigen, Alpha lactalbumin, Immunoglobulins, CEA, Epidermal growth factor receptor, Thyroglobulin, PSA, Cytokeratin's, Oestrogen receptor, Progesterone receptor, HER2/NEU, NMP22, Fibrin, BTA	[18-21]
2. Hormones	Catecholamines and metabolites Human chorionic gonadotropin Antidiuretic hormone Parathyroid hormone Calcitonin Insulin-like growth factors	[22-25]
3. Oncofetal Antigens	Alpha-fetoprotein Carcinoembryonic antigen	[24,26,27]
4. Isoenzymes	Prostatic acid phosphate Neuron- specific enolase Regan ALP isoenzyme Lactate dehydrogenase-1	[28-31]
5. Mucins and another Glycoprotein	CA-125 CA-19-9 CA-15-3	[32]
6. Oncogenes	Src N-myc H-ras. K-ras, N-ras FGFR3 PIK3CA	[33-35]
7. Lipid associated	Polyamines Glycolipids Sialic acid	[36]
8. Some host responses also act as a tumor biomarker	Ferritin Immune complexes Some enzymes such as Lactic dehydrogenase (LDH), Glutamate dehydrogenase (GDH), Creatine kinase (CK-BB).	[37-40]
9. Immune complex	IgM, IgG, IgA, CIC	[41]
10. Glycoprotein	Human chorionic Gonadotropin-Beta, CA-125, CA15-3, CA27-29	[42]

Clinical importance of tumor markers

Tumor biomarkers are of key importance in prognostics, diagnostics, effectiveness of a treatment, pharmacodynamics and reoccurrence of the disease [51-53].

Tumor markers play a crucial role in the assessment of a patient in multiple areas including diagnosis, detection, and differentiation of one tumor from other or to check acuteness of tumor. All of these assessments help the clinician to plan the appropriate treatment and therapy. Tumor biomarkers are used to predict the response of the patient toward treatment by checking the level or presence of the marker [54]. Tumor markers are of vital importance in the synthesis of cancer medicine against a specific cancer type [51-55].

Biomarkers are widely studied during assessment of an individual's risk of developing inherited cancer. BRCA1 is a prominent marker in the identification of cancer in families having a history of ovarian cancer [55].

A biomarker is used to check which therapy is most suitable for cancer. For example, EGFR is shown poor response against Kirsten Rat Sarcoma Virus (KRAS) gene that are associated with colorectal cancer which indicates that this is not suitable therapy against colorectal cancer therapy [55].

It also plays a role in monitoring the response of patient against therapy. Some markers such as Carcinoembryonic Antigen (CEA), cancer antigen 125 (CA125), and Cancer antigen 15-3 (CA 15-3) are used in the monitoring of different cancers including breast cancer.

It can also be used in prognosis. Now there are different gene expression signatures that have been used to estimate prognosis. **Table 3** shows the role of tumor biomarkers in different cancers.

Classification of Tumor Biomarkers

Cancer biomarker is classified on the basis of their role, this classification is independent of the nature of biomarkers. It depends upon the role that they mainly played in the different prospects of disease. For example, some biomarkers play role in the prediction of an action of specific drug against specific cancer, so they are called

predictive biomarkers. Some biomarkers help the clinician to take the right decision and approach to treat the specific cancer, called prognostic biomarkers, some biomarkers indicate the presence of specific cancer, called diagnostic biomarkers, and some are involved in the pharmacodynamics by playing a role in the selection of dosage. So, tumor biomarkers are classified in to four categories including prediction, prognostic, diagnostic and pharmacodynamics.

Prognostic biomarkers

Prognostic biomarkers may not help the clinician for choosing the drug best for the individual, instead it can directly provide the information about clinical outcome, cancer progression or its recurrence in the future [65]. So, it can help the clinicians to decide specific approaches for the treatment of cancer [66]. With respect to this there are different genomic tests that are commercially available to help the clinician in the treatment as well as therapeutic decision. Oncotype DX, AviraDX and, Mamma print are the popular genomic tests available that help the clinician to take a decision on the basis of genetic expression readout of individual patient. For example, 21-gene recurrence score assay predict the breast cancer and its recurrence [67].

Predictive biomarkers

Predictive biomarkers or response biomarkers are the dominant factors that play a role in the choosing the specific drug which is proven best for the treatment of individual. Responses are shown whether in the form of activation / deactivation or in the form of overexpression of specific markers [68]. These all indicate the effect of treatment on individual afterward clinician decide whether this drug is useful or not for the patients. For example, response of trastuzumab drug in breast cancer is predicted by the activation of HER2 protein, similarly HER2 is overexpressed when a patient is treated with Herceptin drug [68,69] Likewise resistance of Epidermal Growth Factor Receptor (EGFR) inhibitor in colorectal cancer is indicated by the activation of KRAS mutation. Some mutations in specific genes also help to predict the specific treatment such as mutation in EGFR gene indicates that these two drugs (erlotinib or gefitinib) are applicable for the treatment of lung cancer [69].

Role	Example	Cancer type	References
Monitor or progression in metastatic disease	CA 15-3 and CEA	Breast Cancer	[56]
Estimate the risk of developing cancer	BRCA1 germline mutations	Breast cancer and ovarian cancer	[57]
Monitor the reoccurrence	CEA	Colorectal cancer	[58]
Predict response to therapy	Estrogen receptor expression	Breast cancer	[59]
	HER2 expression and anti-HER2 therapy	Gastric and breast cancer	[60]
	KRAS mutation and anti-EGFR antibody	Colorectal cancer	[61]
Screening	Prostate specific antigen	Prostate cancer	[62]
Differential diagnosis	Immunohistochemistry to determine tissue of origin	For all cancers	[55,63]
Determine the prognosis of disease	21 gene recurrence score	Breast cancer	[64]

Diagnostic biomarkers

Some biomarkers expression indicates the presence of a specific disease in a patient and these markers are called diagnostic biomarkers. In cancer, some cases reported that these diagnostic biomarkers are present in every stage, so it is also considered that they may be helpful to determine the condition of patient, and stage of cancer. For example, calcitonin hormone expressed in the early stage of medullary thyroid cancer [70]. Recently, a bladder tumor antigen and nuclear matrix protein-22 are two biomarkers approved by US Food and Drug Administration (FDA) as a diagnostic biomarker for the bladder cancer [69,71].

Pharmacodynamics biomarkers

Pharmacodynamics biomarkers are expressed to indicate

the effect of a drug in an organism, this indication help the clinician to decide the accurate dosage of the drug for the patient. Pharmacodynamics biomarkers can also be used to examine the drug effect, tumor response, and help to regulate the routine of the drug course [72]. Combining effect of drug with pharmacodynamics markers enhance the effect of drug as well as protect the patient for irrational dosage. To making this type of combining effect there are two biomarkers program that have been set up to support NExT drug developing projects, one is “Imaging” and another is “Clinical Assay Laboratories”. These two programs allow the Accurate screening of pharmacodynamics biomarkers and overall bio distribution of Palladium compounds [65,72].

Table 4 shows different biomarkers on the basis of their classification.

Biomarker Name	Cancer type	Classification/Role of biomarkers	References.
Squamous cell carcinoma (SCC)	Head and neck cancer	Play role as a predictive, diagnostic, and prognosis biomarker.	[73,74]
Cyfra 21-1	Head and neck cancer	Prognosis, and good candidate for diagnosis.	[75,76]
Carcinoembryonic antigen (CEA)	Lungs cancer	Diagnostic, predictive, and prognosis biomarker.	[77]
Squamous cell carcinoma (SCC)	Lungs cancer	Its high concentration predicts the lung cancer, but not a best candidate marker for diagnosis and prognosis.	[78,79]
Alpha-fetoprotein (AFP)	Liver cancer	Diagnostic and prognosis biomarker. Predicts advanced tumor stage.	[80,81]
Beta ₂ -fetoprotein	Blood cancer.	Diagnostic biomarker, its high level is linked with poor prognosis.	[82,83]
Carcinoembryonic Antigen (CEA)	Colon and Rectum cancer	Predictive biomarker, and diagnostic in advanced stage.	[84,85]
Carbohydrate antigen 19-9 (CA 19-9)	Colon and Rectum cancer	Elevated level in serum is used for diagnostic purpose. It also plays role as a prognostic and predictive biomarker.	[86,87]
Carbohydrate antigen 50 (CA50)	Colon and Rectum cancer	Prognosis and diagnosis biomarker.	[88]
Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP)	Prostate cancer	It plays role as a diagnostic, predictive, prognosis, and pharmacodynamics biomarker.	[89,90]
Beta-HCG	Testis cancer	Diagnostic and prognosis biomarker.	[91,92]
AFP	Testis cancer	Prognosis, diagnosis, staging, and surveillance biomarker.	[93,94]
SP-1	Testis cancer	Play dominant role in diagnosis, but also play a role in prognosis. SP-1 also play an important role in the diagnosis, prognosis, prediction, and pharmacodynamics of pancreatic adenocarcinoma.	[95,96]
5-Hydroxyindoleacetic acid (5-HIAA)	Nervous System	Pharmacodynamics, predictive and prognosis biomarker.	[97]
Calcitonin	Thyroid cancer	Help in earlier diagnosis, pharmacodynamics, prediction, and prognosis.	[98,99]

Thyroglobulin	Thyroid cancer	It is good but not a perfect candidate for diagnosis and prognosis. But helpful for prediction as well as pharmacodynamics.	[100-102]
CEA	Thyroid cancer	Good for diagnosis, but may be not good for prognosis and prediction.	[103,104]
SCC	Esophagus cancer	Diagnostic, poor candidate for prognosis.	[105,106]
CEA	Breast cancer	Prognosis, predictive, pharmacodynamics, and also play a diagnostic role along with other three biomarkers including BCL2, CA15-3, and HER2, but individual specificity for diagnostic purpose of CEA is less as compared to the combining specificity with CA15-3. CEA level higher in HER2 positive tumor patient. Not a good candidate for metastasis information.	[107-110]
Cancer antigen 15-3 (CA 15-3)	Breast cancer	Diagnosis, CA15-3 is more specific for diagnostic purpose than CEA. CA15-3 level elevates in ER negative tumor patient. Useful for Prognosis, but not a standard marker. Useful for Earlier detection, not good for screening. Elevation of CA15-3 linked with tumor size.	[108,109,111,112]
Mucin-like carcinoma-associated antigen (MCA)	Breast cancer	MCA along with CA15-3 is an excellent candidate for determining the cancer metastasis. Along with other biomarkers like CEA, CA15-3, is a Good candidate for prognostic and diagnostic purpose.	[113,114]
BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2)	Breast cancer	Diagnosis, paly important role in selection and management of chemotherapy.	[115,116]
Estrogen and Progesterone Receptor	Breast cancer	Play significant role in selection and management of Hormonal therapy, serves as a predictive and pharmacodynamics biomarker.	[117-119]
CEA	Stomach cancer	Serves as a prognosis, predictive, and diagnostic marker.	[120,121]
Cancer antigen 72-4 (CA 72-4)	Stomach cancer	Highly specific for diagnosis than any other biomarkers used for stomach. It is also considered as a best predictive maker but in combination with other three markers (CEA, CA 19-9, HCG beta). Play a role in monitoring along with two other biomarkers (CA19-9, CEA).	[122,123]
CA 50	Stomach cancer	Play an important role in prognosis, diagnosis. In combination with CA19-9 play dominating role in the earlier detection of gastric carcinoma. CA 50 with CA19-9 and CEA shown poor prognosis before surgery.	[124,125]
CA 19-9	Pancreas cancer	Prognosis, diagnosis, and also play role as a predictive biomarker.	[126]
Elastase	Pancreas cancer	Diagnosis marker, low level linked with poor survival.	[127,128]

CEA	Ovary cancer	CEA is an excellent earlier diagnostic biomarker, its specificity and sensitivity increase by combining detection with CA125, and CA199.	[129,130]
Cancer antigen 125 (CA 125)	Ovary cancer	Play role as a diagnosis, predictive, and prognosis marker. One of the drawbacks is, it also elevates in individuals without ovary cancer.	[131,132]
AFP	Ovary cancer	Diagnostic, prognostic, and predictive biomarker.	[133,134]
Beta-HCG	Ovary cancer	Play role in prognosis and diagnosis, present in high level in stage 3 and in stage 4.	[135]
SCC	Cervix	Prognosis, diagnosis, and predictive biomarker.	[136,137]

Types of Tumor Biomarkers

Tumor biomarkers can be genetic or epigenetic. Some are even secreted only when a specific protein or hormone is over expressed.

Genetic and epigenetic base markers

Genetic and epigenetic mutations also help to determine a specific cancer type [138]. Mutations in the genes encoding tumor protein p53 (tumor suppressor gene) [139], *KRAS* or *epidermal growth factor receptor (EGFR)* are the prominent genes in case of esophageal, liver, lungs, pancreatic, and colorectal cancer [140-142]. Mutations in *BRCA1* & *BRCA2* are the prominent in the case of breast and ovarian cancer [143]. Epigenetic alterations include methylation in many tumor suppressor genes. For example, genetic and epigenetic alterations affecting of P14ARF and P16INK4A protein found in the patient of oral squamous cell carcinoma, and laryngeal squamous cell cancer patients [144]. All these genetic and

epigenetic mutations help diagnose a specific cancer type.

Role of genetic mutations in cancer research and in medical science

Various genetic mutations help to determine the specific cancer type. These types play a role in diagnosis, treatment, therapy, and also help to check the response of patient towards treatment. Some genetic mutations are shown in **Table 5** and **Table 6**.

Both tables explain the region of the marker, its nature, type of cancer in which specific biomarker is present, sample collection site, and its usage i.e., how these markers play different roles in diagnosis, treatment, and monitoring. **Table 5** explains the gene mutation based biomarkers whereas **Table 6** is based on protein, hormone, and enzyme based biomarkers.

Overexpression of some proteins and hormones are also used as potential tumor biomarkers. Some of them are list in **Table 6**.

Table 5. Genetic mutations.

Mutated Gene Name	Normal function of this mutated gene	Common in Cancer Type	Sample Area	Usage	References
Anaplastic Lymphoma Kinase gene (ALK)	Cell growth	Anaplastic large cell lymphoma, lung cancer, and neuroblastoma	Tumor region	Play important role in prognosis and treatment	[145]
AFP	Immune regulator protein	Liver cancer	Blood	Prognosis, diagnosis, and check response of patient towards treatment	[146,147]
<i>BRCA1</i> and <i>BRCA2</i>	Suppress cell growth	Breast, ovarian, and prostate cancer	Blood	Determine the risk, treatment and therapy	[148,149]
<i>B-RAF</i> gene	Signaling in cell & in cell growth	Colorectal, cutaneous, and melanoma cancer	Tumor	Treatment and therapy	[150,151]
<i>BCR-ABL</i> fused gene	Linked with cancer	Leukemia	Bone marrow or blood	Diagnosis and monitor disease status	[152,153]
<i>CD117</i>	Bind with other to play a role in blood cell growth	Mucosal melanoma and gastrointestinal stromal tumor	Tumor	Diagnose and treatment	[154,155]

Tumor biomarker Name	Nature	Common in cancer type	Sample area	Usage	References
Thyroglobulin	Hormone	Thyroid cancer	Blood	Diagnosis	[156,157]
Prostate specific antigen	Protein	Prostate cancer	Blood	Diagnosis, response, and recurrence	[158,159]
Lactate dehydrogenase / beta2-microglobulin.	Group of enzymes	Lymphoma, leukemia, and melanoma	Blood	Assess stage, prognosis, and response to treatment	[160-162]
HER2	Protein	Brest, ovarian, gastric cancer, and pancreatic cancer	Tumor	Determine about appropriation of therapy	[163]
HE4	Protein	Ovarian cancer and endometrial cancer	Blood	Treatment, prognosis, diagnose and monitor for recurrence	[164,165]
Chromogranin A	Protein	Gastroenteropancreatic Neuroendocrine Neoplasm	Blood	Treatment, prognosis and monitor for recurrence	[166]

Identifications Methods

Biomarkers are a source of identification not only limited to specific disease. They are present in different parts of the body depending on the progression of the disease. After excretion these biomarkers become part of the blood, urine, and cerebrospinal fluid. Some biomarkers also become part of the respiratory system and become a source of identification, for example acetone smell indicate the high sugar level in the body and detected through the smell from the mouth of patient. Biomarkers may be protein, metabolites, hormone, lipids, and some genomic expressions as shown in **Table 2**. On the basis of these types, identification technique varies. For example, If the biomarkers are protein in nature then the diagnostic techniques are protein based. Similarly, if the maker is a metabolite than the technique will be like wise, and if biomarkers is a genomic expression than technique will be genomic based such as DNA micro arrays, PCR-based, fluorescence *in situ* hybridization etc. Details of all of these identification techniques on the basis of their nature is available on (The handbook of biomarkers, Springer). Some important techniques that are commonly used for the identification purpose and are not mentioned in The handbook of biomarkers is given below.

Gene expression array

Gene expression profiling technique is used to check the expression of numbers of genes at once [167]. Human cells differentiate on the basis of their expression, only a small subset of gene expression makes one cell different from the rest. So, gene expression profiling technique utilizes the DNA microarray technique to evaluate the expression of these genes [167].

In this technique, a series of microscopic spots of Probe is attached to the gene chip. Target tumor DNA obtained by tumor biopsy is hybridized to the complementary sequence on the gene chip. After scanning the strength of fluorescence at every spot provide the detail about the level of expression of the particular gene [168].

The combination of long oligonucleotides (probe) with chemiluminescence gives more accurate results than any ordinary method [169]. Because long oligonucleotide enhances the specificity, detection, and binding property of the gene expression

profiling technique compared to the normal techniques [169]. For further analysis and validation process, the system is combined with different standard database or tools to know more details and check the validation of specific gene or specific gene related research [167-169].

Common Proteomic technologies

After whole genome sequencing protein analysis is another important aspect to study the differential expression of genes [170]. A Recent study on fragmentome and peptidome provide important information about physiology and disease processes [171] Fragmentome and peptidome are the small protein fragments present in plasma and these fragments play role as a proteomic biomarker. So, in future, this type of protein-based biomarkers plays important role in detection, diagnoses, and treatment of tumors [171].

There are different approaches that are currently used in the area of proteomics such as 2D gel electrophoresis [172], Isotope coded affinity tag, 2D PAGE, mass spectrometer, Imaging mass spectrometer, MALDI mass spectrometer, Quantitative mass spectrometry and real time PCR are the notable technologies that are currently used in the area of proteomic study [171,172].

High-throughput sequencing

High throughput sequencing is able to perform sequencing of multiple number of DNA molecules at once [173]. Though this advantage, HTS is able to create large data sets and generate cellular genome and transcriptome signatures of various diseases [171]. This sequencing also plays a dominant role in the identification of novel variation and mutations, and because of this property, it is extensively used in tumor study. So, in near future, all these techniques play a prominent role in the elimination of deadliest disease like cancer [171,173].

Immunological detection.

Identification of tumor biomarkers by Immunological detection method is based on interaction between localize specific antigen on tumor marker with monoclonal and polyclonal antibodies, usually monoclonal antibodies is used because of their specificity [174]. Antigen consist of specific antibody binding sites, this specific

binding site composed of saccharides or amino acids knows as epitopes. A tagged antibody binds to the specific localized antigen present on the surface of cell either by electrostatic interaction, or by hydrogen bond or by van der Waals interactions. After the attachment, tag is identified by either immunohistochemistry technique in which chromogen is used for visualizing purpose or by radio-immuno assay in which radio tag is used or by enzyme-linked immunosorbent assay in which enzyme is used to color the product, intensity of color define the amount of bounded antigen [174,175].

Uses of Biomarkers in Cancer Research

Use in the target drug delivery

Surface plasmon amplification by stimulating emission radiation known as (Spaser) is a 22 nanometer plasmonic Nanoparticle, used for the detection as well as eradication of tumor cell with accuracy [176]. Its properties include water solubility, super intense fluorescence, low toxicity, biocompatible, and target specificity make it a dominating nanoparticle for the future treatment [176-178]. Its composition includes plasmonic nano-particles surrounded by the silica, covered with uranine dye [179,180]. To make spaser target specific, it is attached with molecular biomarker so that it is able to target the specific cell, for example in the case of breast cancer, folic acid attached to the spaser surface. Then this spaser is only attached to those cells where this marker receptor is overexpressed. Folic acid receptor is overexpressed in the breast cancer cell rather than the normal cell, so this biomarker makes the spaser target specific [176].

Intake of spaser is simple, either by injection or drinking. Afterward it becomes part of the blood and sticks on the surface of tumor cell. Its sticking specificity is based on selective molecular targeting biomarkers. After sticking it absorbs laser light and rises its internal heat which plays a role in the production of shock waves that destroy the cancer cell [176-179].

Development of specific drug based therapy

Biomarker based drugs account for a reasonable percentage of the drugs used in treatment of cancer. A range of biomarker-based drugs have been approved by US Food and Drug Administration (FDA) for the treatment of various human cancer types. Some biomarkers are same in different cancers but the difference is on the basis of concentration or site of the tumor.

Limitations of Tumor Biomarkers

Keeping in mind the number of onco drugs based on biomarkers, their role in cancer studies cannot be underestimated. However, biomarkers are not preferred to specifically or sensitively detect a tumor, especially in the early stages of the cancer, as many biomarkers can lead to false positive results [181].

Tumor biomarkers play a crucial role in diagnosis and monitoring of cancer. Some tumor biomarkers are specific to an organ while some are not, for example CA 19-9 is considered as specific to the pancreatic cancer but it is not specific for this cancer so it gives non-accurate results [182]. Tumor biomarkers may be helpful for the monitoring of cancer but it is not accurate for the diagnosis purpose [182]. Some previous research shows that biomarkers are not useful in diagnosis or even in monitoring of cancer such as CEA in colon or breast cancer, HCG in breast cancer, CEA, ACTH, ADH, and Calcitonin in Bronchogenic cancer, AFP,

HCG in Nonseminomatous testicular cancer, Acid phosphate in prostatic cancer, and Immunoglobulin in multiple myeloma [183]. In the beginning of 21st century new biomarkers have been identified which refute the previous concept about biomarkers by playing a revolutionary role in the diagnosis or in the management of cancer treatment [184].

Conclusion

A tumor marker is a substance used as an indicator of a tumor. The nature of tumor biomarkers is not defined, but they represent the presence of a specific tumor. Elevation or decrease in the concentration of marker plays an important role in detection of a specific tumor. There are different identification processes that are currently in use to identify the cancer including gene expression array, proteomic technologies, and high-throughput sequencing. This detection plays a crucial role in treatment, prognosis, and to measure the effectiveness of the treatment, tumor biomarkers are also used to check the recurrence. Now biomarker is playing an important role in medical research especially in drug development processes against tumor. Somehow, it is considered that tumor biomarker is good only for monitoring purpose but not for diagnostic purpose.

Future Prospect

Through the development of druggable targets, biomarker also plays an important role in the new drug therapies. Now researchers are developing proteomic based biomarkers to identify cancer in the earlier stage rather than the end stage. In future, researchers will sequence the whole genome of the mutant region in cancer that codes the mutant protein and cause cancer. It will make cancer easy to cure in the very early stage.

It is also possible to make a specific frequency/specific labeled biomarker-based nanoparticle whose frequency is same with respect to deregulated cell. After reaching the specific deregulated cell, the frequency of nanoparticle increases and creates resonance as a result destruction of the cancerous cell occurs without damaging the normal cell. Or in future, it may also be possible that researchers would be able to make a drug that can make proof reading gene p53 active that is deactivated by cancer cell and not allow cancer to reduce the expression of tumor antigen and increase the production of interferons and interleukins.

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