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Review

Oncoproteomics: Opportunities, Challenges & Advanced Technologies

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Abstract: Oncoproteomics is nothing but the analysis of proteins and their interactions in a cancer cell through proteomic technologies. Oncoproteomics is playing a progressively significant part in diagnosis and the management of cancer. It also helps in the advancement of personalized therapy of cancer. Oncoproteomics holds great potential not only for opening the complicated molecular episodes of tumorigenesis but also for those that regulate clinically essential tumor habits, like metastasis, invasion, and resistance to treatment. Protein molecules show a significant impact on the evolution of cancer as it mainly develops due to abnormal signaling pathways. Detection and comprehension of these alterations is the major concept of oncoproteomics. Novel proteomic technologies related to cancer are defined in short, which are assisting not only in the comprehension of the mechanism of drug-resistant in cancer but also bestow some guides in management. For the diagnostic and prognostic categorization of the disease condition, and in measuring the drug efficiency and toxicity acclimatization of proteomic technologies in clinical laboratories is the fundamental objective of oncoproteomics. A considerable influence on the management of cancer patients and on a spectacular revolution in cancer research might notice by data obtained through such novel technologies. For the cancer therapy, the identification of novel targets, as well as an understanding of tumor development, might permit by the research of tumor-specific proteomic profiles. A wide perspective on drug-resistant and anticancer drug discovery, proteomic biomarkers and its function in the diagnosis of cancer, current innovation in proteomic technologies have tried to give in this review.

Keywords: Oncoproteomics; Nanooncology; Cancer biomarkers; anticancer drugs; personalized medicine

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1. Introduction

In current days, the human race is disturbed by one of the most considerable universal health apprehension symbolized by cancer. With the increasing growth and aging of the world's residents, the overall load of the cancer is predicted to rise and globally the condition is set to worsen because cancer not only disturb the developing nation but also developed nation [1]. With cancer, more than 11 million individuals are detected every single year. As per the prediction, every year there will be 16 million fresh cases by 2020. In worldwide mortality, cancer contributed 7.6 million (or 13%) in 2005, from a total of 50 million demises universally. Loss due to cancer in the universe is estimated to continue growing, as per prediction in 2015 due to cancer 9 million individuals died and 11.4 million human being will die in 2030 [2-3].

A few years ago the extent of complexity of the illness which was not evident, has been exposed due to the increase in basic knowledge about cancer. For instance, for given cancer categories (e.g. leukemia and breast) the figure of molecular subtypes identified is increasing rapidly, in terms of not only the cell type but also the differentiation status and its interaction with tumor microenvironment the daunting heterogeneity of tumor cells is not yet fully understood, and application as well as evaluation of novelties as well as in the clinical supervision of cancer victims the ever-increasing need for multidisciplinary has become the more complex. A successfully increase in cure rates, may only be accomplished by combined collaborative activities focused on enhancing therapeutic strategies and prevention which helps in a noteworthy relief of the cancer load, in the short-range. If malignity is identified in advance i.e. when they are confined to a minor area and are still small, cancer can be managed more successfully and with fewer morbidity for victims as well as a key link between treatment and prevention is expected to be provided via advance diagnosis.

Novel biomarkers as well as targets for drug discovery, will be recognized as our awareness of the biology concealed in the malady pathogenesis improves, specifically with the signaling mechanism which are disturbed in tumor cells and "the right drug for the right patient at the right time" i.e. the personalized cancer treatment, are expected to be results from these innovative molecular targeted treatments. In this manner, to impart functional insight for generating innovative targets for drug development and companion diagnostics, and to characterize as well as define functional and regulatory networks proteomic technologies are estimated to perform an important character because they offer crucial measures [4].

2. An outline of proteomic technologies in Cancer Research

Molecular modifications which take place in a cancerous cell can be noticed as biochemical alterations demonstrated on a protein level. More than 20,000 proteins are assessed to be involved in the human proteome. A plethora of vital mechanisms involved in functionality as well as cell signaling can be exposed by the reviewing proteins that are differentially expressed in cancer cells. In cancer research, there has been a noteworthy rise in proteomics-based research, particularly, within the last 20 years. The applied proteomic research application dates back to the early 2000s [5-6]. The reorganization of abnormal as well as inadequate proteins in exceptional materials is possible because of a number of growing scientific progress which has increased our understanding of oncoproteomics [7-9]. In cancer research, proteomic approaches are progressively being used as a result of data management,

better-quality equipment, and computer algorithms in combination with the integrative understanding of oncogenic signaling pathways [10-14].

The original version of the study of cancer built on protein identification has changed to protein functional analysis because of the complexity of cancer [15]. Because of this, the cancer research has transformed to the comprehension of complicated oncogenic signaling route which was formerly based on the discovery of a single cancer biomarker [16-17]. The measurement of specific proteins in samples with high assurance, the identification of post-translational protein alterations (e.g., phosphorylation, glycosylation, as well as oxidation) and the study of protein-protein interactions, are facilitated by strong and potent techniques presently used in proteomic research. For this objective, evolving analytical approaches comprise nanoproteomics, tissue microarray, cancer immunomics to identify autoantibody signatures, aptamer-based molecular probes, and antibody microarray.

2.1 Nanoproteomics

In the advances of oncology, an important role has been played by nano-oncology, which is the application of Nanobiotechnology to cancer [18]. The early diagnosis of cancer and the discovery of biomarkers of cancer is enabled by molecular diagnostics and proteomics which is refined by nanobiotechnology. For various technical challenges in proteomics as well as molecular diagnostics based on protein, a solution was provided by the nanomaterials [19]. In proteomics, by the use of nanoscale devices such as nanofluidics and nanoarrays, the improvement in the oncoproteomics study has been seen. The nanoscale analysis is subjected to low abundant proteins as well as those proteins that are extracted from limited source materials for e.g. biopsies. Mass analysis of peptide fragments leads by the nano-capture of particular proteins as well as complexes, and development of entire subsequent specimen handling stages, with single protein reorganization accuracy at the low zeptomole level. This is a much-focused method and also called as targeted proteomics, which includes the inspection of subsections of the proteome for e.g. the proteins which exist as a member of higher order complexes or those proteins that are either characteristically altered, or fix to a specific DNA structure, or a combination of thereof. To recognize how cancer genetics determinants modify cellular physiology as well as respond to agonist's, nanoproteomics can be used, which will help in cancer for the development of personalized therapy.

2.2 Tissue microarray

In oncology, for the analysis of molecular biomarkers, a tissue microarray (TMA) is a high productivity tool. In a single microscopic slide analysis of up to 1000 tissue samples is enabled by the tissue microarray. For the detection of cancer biomarkers, development of diagnostic tests and for the study of tumor biology TMAs are very useful [20]. Laser capture microdissection can be combined with tissue proteomics. For oncoproteomics TMAs are a useful tool. From formalin-fixed paraffin-embedded prostate cancer tissue samples, to identify proteins without deviation direct tissue proteomics can be used [21]. For testing of breast carcinoma for human epidermal growth factor receptor 2 (HER2) status, and to compare favorably with fluorescent in situ hybridization and with immunohistochemical, TMA technology has been applied [22].

2.3 Role of cancer immunomics in identifying autoantibody signatures

In cancer, the increased incidence of autoantibodies is well known. In the presence of either breast or colorectal cancer as a response autoantibody signatures are produced and cancer immunomics has been

used to identify it. Immunoblotting, image analysis, 2D GE and MS are used to perform serological proteome analysis (SERPA) [23]. An approach has been developed that combines, Nan flow separation of the resulting peptides, and identification, enzymatic digestion of the isolated antigens, 2D immune-affinity chromatography, MAPPing (multiple affinity protein profiling), as an alternative to identifying the antigens recognized by the autoantibodies of the cancer patients. A limited number of proteins reacting preferentially with cancer sera as well as proteins recognized by autoantibodies independently of a cancer status are identified by these approaches.

2.4 cancer proteins and function of aptamer-based molecular probes

Due to the particular 3D structure of aptamer-based molecular probes, they can bind to a given ligand with a high specificity and affinity by which the biological function of ligand gets antagonized. To detect protein signatures of the cells aptamers are used, because of the tendency of short DNA to fold into shapes that bind to specific proteins. The technology can be combined with biochips which will give a method for monitoring protein changes in the blood as an indication of the development of carcinogenesis, for example in women with genetic risk of breast cancer associated with BRCA1 dysfunction.

For T-cell acute lymphoblastic leukemia, as a biomarker protein tyrosine kinase 7 (PTK7), has identified, which is enabled by the use of a two-step strategy, aptamer selection and biomarker discovery, combined with mass spectrometry [24]. The cell-SELEX (systematic evolution of ligands by exponential enrichment) process is used for selection of aptamers for leukemia cells, without any prior knowledge of cell biomarker population, conjugated with magnetic beads and then used to capture and purify their binding targets on the leukemia cell surface. The significant enhancement within the effectiveness of biomarker discovery and the therapeutic approaches to cancer as well as the development of diagnostic tools will be facilitated by this two-step strategy.

2.5 Antibody microarray

Due to the recent advances in proteomics and automation, the use of antibody microarray continues to grow rapidly, and opportunely a high-throughput multiplexed analysis of protein biomarkers is created by this combination. Simultaneous measurement in a single sample of many proteins that work in pathways and a network of cancer has enabled by the antibody arrays [25]. However, for protein, the lack of PCR like amplification methods is a primary limitation of this technology. To quantify protein biomarkers in the femtomolar range, and from limited sample quantities with very high sensitivity, it is necessary to construct assay, to realize the full potential of array-based protein biomarker screening. Combining the advantages of a microarray including the ability to screen very small sample volume, cost saving and higher throughput, and multiplexing capabilities the construction of ultra-microarray has been described by the Scientist at BioForce Nanoscience Inc. [26]. For prostate cancer screening, widely used biomarkers such as IL-6 and PSA were constructed by the antibodies ultra-microarrays. With the detection level in the attomole range using purified proteins, these ultra-microarrays were found to have a high sensitivity and specificity.

3. The function of proteomics in cancers of varies organs

With suitable cases of breast, prostate and lung cancer as well as in leukemia and colorectal cancer the function of proteomics not only in the development of personalized approaches but also in therapy, diagnosis as well as in the combination of both has been described.

3.1 Breast cancer and proteomics

The human epidermal growth factor receptor-2 (HER-2) gene, in the management of breast cancer which is enlarged by 20-30%, is a model of association of therapeutics as well as diagnostics. HER2 lack is related with resistance to therapy, however, its overexpression is linked with respond to Herceptin (Genentech). Fluorescents in situ hybridization (FISH) and immunohistochemistry (IHC) are two ways to determine the HER-2/neu state of primary breast cancer. Patients having breast cancer whose tumor tissue represents the HER2 protein, is identified by an approved IHC test which is HercepTest (DakoCytomation). Interphase HER2/neu gene intensification, is quantitatively determined by HER2 FISH pharmDxTM kit. Improved clinical acceptance to an anthracycline-containing chemotherapy regimen, as compared to the treatment with methotrexate, fluorouracil, and cyclophosphamide when subjected to the intensification of HER2 in breast cancer cell is shown by the National Cancer Institute of Canada by Mammary5 trial [27].

Nevertheless, because of some technical issues, tests applied in initial phase breast cancer might not precisely reflect in metastatic tumor with regards to HER-2/neu status. If 30% or more of the cells are 3+, then tumors should be designated as HER-2/neu positive as suggested by the guidelines. With the aid of authenticated test, in serum, the circulating levels of the HER-2 extracellular domain can be determined and above 15 ng/ml, increased level of serum HER-2/neu displays advancement in breast cancer [28].

3.2 Prostate cancer and proteomics

Biomarkers for the identifying, checking as well as characterizing the signaling phenomenon inside the actual human biopsies will be critical for patient-tailored treatment with the advent of molecular targeted therapeutics. The most powerful method which might expose the regulation of gene that can’t be identified on a genetic level as well as for the analysis of cellular protein phenotype, 2D gel electrophoresis remains the most potent technique, although several non-2D gel electrophoresis technologies are available for study in prostate cancer proteomics.

A prostate-specific antigen (PSA) which is an androgen-regulated gene, as well as numerous innovative complementary DNAs, has been displayed by the prostate cancer gene expression researches. 2D gel electrophoresis has generated profiles of protein expression belonging to androgen-stimulated cells of prostate cancer. On human prostate tissue cells, the assessment of the number of PSA molecules/cells has been performed by linking LCM with sensitive quantitative chemiluminescent immunoassay. Alterations in expression of PRDX4, FKBP4 as well as FLNA (7-15) have been established through immunoblot analyses, in addition for generating an extra intact outline of prostate needle biopsy specimens a method build on proteomics is applicable [29]. For treatment and diagnosis of prostate cancer, the useful molecular target is provided by this approaches.

3.3 Lung cancer and proteomics

Presently, for accomplishing the objectives of determining a therapy and assessing prognosis, the pathological, as well as the clinical staging of lung cancer, is unsatisfactory. Because of the technical advancements within proteomic as well as genomic analyses, in addition to their implementation in the prognosis and diagnosis of cancer of lung, crucial developments in comprehension of the molecular basis of lung cancer has been created. A straightforward as well as noninvasive technique, which is exhaled breath condensate collection, by sampling respiratory track fluid it assists the study of numerous biomarkers comprising proteins and may be applicable in finding of lung cancer [30]. For diagnosing the persons at the great possibility for lung cancer and also in suggesting the diagnosis for same, a group of four serum proteins (squamous cell carcinoma antigen, alpha 1-antitrypsin, retinol binding protein, and carcinoembryonic antigen) are appreciated [31]. Potential therapeutic targets can be provided through if a trustworthy protein profile is recognized that is linked to inferior detection. To enable a personalized treatment, before the clinical manifestation of lung cancer for its diagnosis the evolvement of straightforward serum test is practicable which may also concurrently detects the chemotherapeutic drugs to which the tumor is susceptible [32]. Prior to the implementation on advancement in the management of patients with lung cancer which can be evaluated adequately, there is a necessity for transforming the technology from bench to the besides as well as additional developments in sample preparation methods.

3.4 Leukemia and proteomics

Because, the cytogenetic analysis is time-consuming and it is expensive, to subclassify leukemia proteomics is being used. To rapidly identify different type of leukemia several useful protein biomarkers have been discovered: annexin 1, tropomyosin 3, peroxiredoxin 2, catalase, annexin A10, RhoGDI 2, alpha-enolase. For disease prognosis as well as an outcome they can be used as biomarkers which are differentially manifested in acute myeloid leukemia (AML) [33]. For treatment of AML based on rational pathogenesis, they offer potent novel targets.

In AML, the total survival of patients remains disappointing regardless of massive therapeutic attempts which range from allogeneic stem cell transplantation to numerous cytotoxic agents. In AML, the discovery of novel biomarkers, as well as therapeutics, will be developed by the interpretation of the AML- specific proteome which also assists in the evolution of personalized management. Limitations in protein detection sensitivity are one of the major challenges, as several regulatory proteins that are essential in response to treatment found in a small amount, which represent a challenge [34]. The opening of new avenues for personalized molecular therapy for AML as well as improvement in efficacy and reduction in toxicity of present therapy are expected to happen due to ongoing developments in proteomic technologies.

3.5 Colorectal cancer and proteomics

A maximum number of the carcinomas of the colon is still identified at a far ahead phase when prognosis is reduced, despite colonoscopy and fecal occult blood test which are existing screening method for colorectal cancer (CRC) which have contributed a reduction of mortality and early detection. With high specificity and sensitivity, a dissimilarity between the cancer patient and healthy patient is enabled by the proteomic technologies, which could also greatly improve the classification systems for CRC as well as its early detection [35]. Utilizing SELDI-TOF MS followed by a classification of three pattern analysis of CRC by a serum protein profiling appropriate technique for identifying novel serum

biomarkers has been defined [36]. In supervising the disease and the therapy these biomarkers play the crucial character. With the optimum goal of tailoring treatment to a tumor profile and to an individual patient as well as to decrease toxicity and improve response rate, there is still a necessity to recognize a panel of predictive markers. From the bench to the bedside the application of proteomic skills for CRC is yet to be transmitted.

The most general phenomenon and the main harmful reason of the CRC is the metastasis. 2D GE joined with matrix-assisted-laser-desorption/time of flight (MALDI TOF) MS was used to conducted differential proteome analysis of two CRC cell lines [37]. With varying potential for metastasis, obvious changes were sensed between the protein profiles of colorectal cell lines. In progression and metastasis of CRC, an important role was shown to be played by the overexpression of heat shock protein (HSP) 27.

4. The function of proteomics in drug discovery of cancer

In traditional drug discovery to rectify some of the scarcities, proteomic technologies are being utilized as an effort. In malignancy, as there are deficiencies in the protein machinery of the cell, that's why proteins become the vital targets for drug discovery, predominantly in cancer. To estimate the effect of a candidate drug on disease state, proteome investigation can be utilized because it can yield a widespread molecular profile of the difference among diseased as well as the normal state. In oncology, for target validation and drug discovery, oncoproteomics incorporated with oncogenomics is the latest tendency [38]. Selection of the finest candidate among novel drug targets, as well as the estimation of all probable protein coding region, has been allowed by the use of proteomics technologies. The anticancer drug target discovery, as well as its validation, has been possible through the identification of modifications definite to the tumor [39]. The prediction of response of the individual patient, identification of disease subgroup, assessment of toxicity and efficacy of the candidate drug as well as the target discovery, all these contributions are made by the human saliva proteomics which might be beneficial for anticancer drug finding [40].

The development of breast cancer which points out by the intercellular signaling pathway, whose study has been assisted by the functional proteomics, will function as a leader for the growth of anticancer drugs. To understand the part of the breast cancer proteome, there is a requirement for innovative technologies for e.g. protein microarray, because with 2-D gel electrophoresis it is unable to reveal it [41]. Within body fluids for quantification of carcinogenic embryonic antigen (a single protein) and for a finding of colorectal, a classic test is founded on proteomics. For prediction of the treatment and disease outcome there is a necessity for supplementary research on genotype-phenotype relationships. To define cell dysfunction in carcinogenesis which is generally not resulted in multiple characters is possible through researches by applying specific tools such as tagged antibodies [42]. In colorectal cancer, there is a need for further development of studies linking large protein expression patterns with the clinical outcome which are still in their infancy. A profile of protein produced by a mass spectrometry and investigated through an artificial intelligence-based algorithm to discover the hidden patterns of combinations of markers which can differentiate cancer victims from healthy once [43]. The implementation of the proteomics methodology, which is created by high-resolution 2-D gel electrophoresis combined with multivariate correspondence analysis as well as mass spectrometry, is used to categorize accurately the biochemical basis of the anti-cancer action of the synthetic cyclin-dependent kinase inhibitor, bohemine, [44]. An advanced resistance of A549 lung carcinoma

cells to bohemine compared to the CEM leukemia cell line is corresponded to the alterations in the protein expression patterns.

3D protein structure determination, laser capture microdissection, protein biochips, as well as protein-protein and protein-drug interaction, these are the most important proteomics technologies accessible for anticancer drug discovery. The important drug targets involved in malignancy are cancer biomarkers and signaling pathways. For developing novel therapeutic agents for cancer, the unlimited possibilities are provided by the wealth of new knowledge in the proteomic database together with bioinformatics as well as a microarray.

5. Proteomics and drug-resistant cancer

Development of resistance to the anticancer drugs in the chemotherapy of cancer is one of the serious trouble. Cross-resistance with a large number of alternative medicines results from treatment with one anticancer drug, in multiple drug resistant (MDR). P-glycoprotein, which is plasma transport protein, is regularly expressed by these MRD cells. A biochemical mechanism such as DNA replication, and repair mechanism or cellular drug transport and detoxification, as well as proliferation status and cell cycle stage, might affect cellular resistance to chemotherapy which is multifactorial. For the reorganization of not only MDR markers but also mechanism, a number of laboratory practices are utilized for an instance polymerase chain reaction, immunocytochemistry, flow cytometry, blotting, and fluorescent microscopy.

In drug-resistant cancer, the involvement of multiple proteins identification has been facilitated by the developments in proteomic technologies. The recognition of differentially expressed proteins among the cells of resistant versus sensitive has been possible by 2D GE, following image analysis as well as MS. When proteins unsuitable expression or structure is responsible for the drug-resistant disease, this may results into advancement in various techniques which will transform the action of such proteins.

In patients with lung cancer, a clinical co-relation to objective response to gefitinib has been recognized as the mutations in epithelial growth factor receptor (EGFR), however, it does not point out resistant to gefitinib. An acquisition of gefitinib resistance has been correlated by the expression of a surface biomarker such as epithelial membrane protein-1, an adhesion molecule. The common mechanism of resistance nominated in a spectrum of cancer cell line, from the various mechanisms of resistance likely present in any given drug-selected cancer cell line have been uncovered by the combined analysis of multiple proteomic types of research of varies drug-resistant cancer cell lines [45]. In the future to get rid of cancer, combination treatments targeting multiple mechanisms to sensitize drug-resistant cancer might be significant, as recommended by this observation.

6. The function of proteomics in molecular diagnosis of cancer

For the detection of cancer, as a fundamental addition over the antibody-based technique as well as genomic, proteomic technologies have emerged. The detection of biomarkers for cancer as well as protein pattern study is the foundation of many of these assay. For the development of individualized therapy of cancer, a significant role has been performed by the nanotechnology through the incorporation of diagnostics with therapeutics, which also permit additional improvements of these tests. For identifying tumor-specific changes in proteins, proteomic separation, as well as analytical practices, have unique capabilities. For the detection of cancer in advance, proteomic techniques have the ability to

identifying molecular markers and diagnostics. During the next decade, these findings will modify the current grading methods and pathological classifications for cancer [46]. The humoral response which is elicited by the tumor-associated antigens whose identification is enabled by the proteomics [47]. From several types of cancer, within the sera, high-frequency antibodies revealed by a proteomic-based approach. Within the clinical application, in determining prognosis as well as in diagnosis and as a novel biomarkers this antigenic protein might work.

6.1 Proteomic analysis of cancer cell mitochondria

In cancer cells, a mutation in mitochondrial DNA has been regularly detected. Until now, the importance of the pattern of gene expression has not been acknowledged. Our knowledge about cancer through research on mitochondrial proteome can be advanced by:

- In cancer cells, detection of atypically expressed mitochondrial proteins is enabled with the help of mitochondrial functional proteomics.
- Targets for therapeutic inventions, as well as for risk assessment and early detection of new biomarkers can be discovered through proteomics.

In gastric cancer cell line of human, increased manifestation of four mitochondrial proteins such as mitochondrial elongation factor Tu, heat shock protein 60, mitochondrial short-chain enoyl-coenzyme A hydratase-1, and ubiquinol-cytochrome c reductase has been revealed by the inspection of the mitochondria enhanced fraction by 2D gel electrophoresis [48]. At the protein level the procedure of mitochondrial alterations in cancer is provided by these findings and in mitochondria, it may function as active cancer biomarkers.

6.2 Diagnosis of cancer by protein pattern

For diagnosis of different cancer the application of proteomic biomarkers is well recognized and as compare to single biomarker protein pattern offer better diagnostic possibilities. Free from the identity of peptides and proteins, the pattern itself is the discriminator as per this approach, and it might also represent a novel diagnostic paradigm. The foundation of pattern determination is the application of machine learning technologies for e.g. neural networks, decision trees as well as different algorithms. The signaling pathways of cancer are known to be managed by post-translational protein alteration, which can be identified with great assurance by the application of high-resolution MS. For comparison of peak pair with a traditional peak pair technique, a model was built from data produced by the use of prOTOF MS on samples from patients with ovarian cancer as well as from cutaneous T-cell lymphoma [49]. The peak pair gave classification equal to superior as compared to a traditional technique that used multiple individual peaks, as shown by the results and in disease process for recognizing of fundamental peak pairs it can be used.

In ovarian cancer for detection of its early stage proteomic profiling has potential. A clear intensification of the sensitivity resulted from combining the CA125 with the recently revealed biomarkers of ovarian cancer progression and in the large control group and ovarian cancer, it should be validated [50]. For ovarian cancer screening as well as for malady monitoring during and after therapy such a multi-marker assay could be suitable.

6.3 Early detection of cancer through serum proteome analysis

The advance diagnosis of cancer is permitted by the identification of biomarker patterns or the new biomarkers through the application of proteome analysis. In serum or other body fluids, the reorganization of secretory products derived from the tumor is allowed through this tool. Besides, in the serum of cancer patients, it might be used to determine the decreased level or loss of proteins, which are usually present in non-cancer patients. Immunological alterations or cancer-specific metabolite are responsible for these changes in serum proteome, which are, at least partially, free of tumor size or mass, and by this means enabling advance diagnosis [51].

In plasma, an increased amount of angiogenic regulatory proteins e.g. endostatin and VEGF are shown by the SELDI-TOF-MS of platelet essence for proteomic profiling but these are absent in plasma. It is not a straightforward relationship with the platelets surface instead it is a selective sequestration method. In human, microscopic size cancer can be detected by this novel property of platelets which is not possible by any presently available diagnostic methods. A detection of a wide range of tumor size as well as tumor type is enabled by this and instead of a single biomarker, it is more inclusive. The tumor movement from its initial in-situ stage throughout its development is allowed by the corresponding modification in the platelets angiogenic profile.

6.4 HER-2/neu oncoprotein as a biomarker for cancer

In the progression as well as in the development of breast cancer an essential part is played by the HER-2/neu oncoprotein which has been revealed by the extensive study for many years. In patients, demonstrating aggressive disease, a high possibility of relapse of malady as well as overall reduced survival, HER-2/neu were displayed as a sign of poor prognosis. In around 30% of a female having breast cancer, a high level of HER-2/neu is found, which is supported by many published studies. In identifying whether that patient has a serious aggressive disease and would, thus, derive substantial profits through additional intensive treatment regimens, determination of patient's HER-2/neu status may be valuable. Besides breast cancer, in numerous other tumor forms such as lung, prostate, pancreatic, colon, as well as ovarian cancers high levels of HER-2/neu are found.

Females displaying recurrent, metastatic breast cancer, the information regarding the HER-2/neu status are not provided by the conventional HER-2/neu testing which is normally restricted to the tissue sample obtained by primary breast cancer. Over the course of the disease, existing estimation of a woman's HER-2/neu status is provided by a less invasive diagnostic tools microtiter plate ELISA HER-2/neu testing with the help of the serum sample. For breast cancer, the result of chemotherapy settled on neoadjuvant anthracycline is significantly predicted by the pre-chemotherapy serum HER-2/neu [52].

7. Diagnostic biomarkers

For the detection of syndromes, the implementation of proteomic technologies is called diagnostic oncoproteomics. Within the significant decrease in a fatality, the advance diagnosis of cancer has a principal role. From victims displaying breast, uterus and ovarian cancer as well as the victims with a benign ovarian tumor, the serum specimen thermo stable fractions has been examined with the help of two-dimensional gel electrophoresis (2-DE) accompanied by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)/TOF MS. In results, the ovarian cancer sample showed a reduction in

transthyretin, while in breast cancer the clusterin, as well as alpha-1-acid glycoprotein, has been precisely down-regulated. Within numerous tumor, the haptoglobin alpha1 was raised, whereas a decreased spot volume was seen with apolipoprotein A-I forms. For small as well as medium protein examination, as a favorable weapon thermostable fraction of serum might be suggested, especially through 2-DE [53].

8. Proteomics biomarkers in cancer

The incomplete understanding of oncogenesis and etiology, as well as the lack of a definite warning sign in early disease, makes the advance diagnosis of cancer challenges. For instance, the less sensitivity of blood tumor marker i.e. cancer antigen (CA) 15-3 for breast cancer makes it unusable for early recognition. For this reason in some nations, for the breast cancer diagnosis, the measurement of HER-2 and carcinoembryonic antigen (CEA) in unusual nipple secretion has been sanctioned [54]. As a response to a therapeutic intervention as well as a signal to the pathological process, the biomarkers can be evaluated as well as objectively measured. Whichever measurable definite molecular changes of cancer cell either on metabolite or protein level, RNA or DNA, is defined as a cancer biomarkers [55]. The dramatic decrease in death is possible by the potential of early diagnosis of cancer. The targets for drug discovery as well as numerous molecular diagnostics of cancer has founded on the biomarkers. The prediction and observing the response to the treatment, determining prognosis, as well as the classification of tumors, is enabled by the fundamental scientific application of cancer biomarkers. Within the tissue, the expression of a definite gene will permit its reorganization accompanied by none of the neighboring cell representing a certain marker. Within last few decades, as per the tumor subtype, a comprehensive classification has been enabled through cancer cells molecular dissection by virtue of profiling of mRNA expression. In table no. 1 the comparison of present tumor marker as well as proteomic biomarkers with their sensitivity and specificity are listed.

Table 1 Difference between the present day tumor markers and proteomic biomarkers

Cancer type	Present tumor markers			Proteomic biomarkers		
	Markers	Specificity	Sensitivity	Specificity	Sensitivity	Reference
Prostate	PSA (Prostate Specific Antigen)	20-34%	86%	97%	83%	56
Ovarian	CA-125 (Cancer Antigen-125)	***	57%	94%	83%	57
Liver	AFP (Alpha-Fetoprotein)	90%	50%	86%	94%	58
Colorectal	CEA (Carcinoembryonic Antigen)	***	43%	93%	91%	59
Bladder	NMP22 (Matritech's nuclear matrix protein)	95%	31%	90-97%	80%	60
Breast	CA 15-3 (Cancer Antigen 15-39)	80-88%	63%	91%	93%	61
Gastric	CEA (Carcinoembryonic Antigen)	***	49%	95%	83%	62
Lung	Cyfra 21-1 (Cytokeratin fragment)	94%	63%	80%	87%	63
Pancreatic	CA19-9 (Cancer Antigen 19-9)	***	72%	97%	78%	64

9. Oncoproteomics and its implementation in the personalized management of cancer

Individualized medicine, for enhancing healthcare of people is emerging concept, which fundamentally means the prescription of not only definite therapeutics but also treatment appropriate for an individual genotype, which is supported by the different factors that impact response to the treatment as well as the disease outcome. The advancement in the individualized treatment of cancer is assisted by progress in

oncoproteomics [65]. The influence of proteomics on cancer will not be constrained to the recognition of advanced biomarkers for early diagnosis as well as novel targets. As per the molecular outline of the cancer cell, the proteomics skills will be utilized to design rational drug and thus the development of initialized cancer treatment is enabled. On the advancement of individualized treatment of cancer, Nano-biotechnology will have an impact on it. In table no. 2 [66] the example of proteomic technologies utilized for personalized cancer treatment are summarized.

Table 2 Summary of proteomic technologies and its application in personalized cancer treatment

Sr. no.	Technologies	Application
1.	Glycoproteomics: in the form of glycoprotein in the cell membrane the biochemical signature of cancer	Molecular targets expressed in tumors for which targeted cancer therapy
2.	To recognize the targets antigen biochemical assay as well as proteomic techniques	For cancer treatment founded on antibody
3.	Fingerprints of laser proteins or peptides founded on mass spectrometry	Molecular classification of human tumor, proteomic outline
4.	Structure determination of protein kinase: in cancer important drug targets	Individualized anticancer drugs screening
5.	A functional map of know cell-signaling networks delivered by reverse phase protein microarrays [67]	For individualization of treatment, for a single patient gained directly through a cancer biopsy specimen correlation of pathways with clinical information as well as biological

10. Challenges and Conclusion

For the detection of cancer and its prognosis as well as for the guidance of anti-cancer therapy numerous proteomics based tests are expected to become accessible. With the usage of proteomics, there are still a lot of challenges associated with the discovery as well as validation of cancer biomarkers. By the use of proteomics, there is no definite cancer biomarker has been documented as well as validated, besides several latest and in process efforts made to detect cancer biomarkers [68-69]. Tumor heterogeneity, the nature of proteomic technology employed, the usage of poor principles for the design of sample collection and studies, as well as the absence of universally standardized proteomic platforms, might be the reasons for this failure [70]. In cancer biomarker studies, unquestionably the main challenges to be addressed are serum proteomics and tumor heterogeneity. In addition, noteworthy obstacles to their usage are low-throughput, the inadequate dynamic range, as well as the high cost of MS-based proteomics [71].

Only a negligible quantity of valuable information has been taking out from proteomic studies, on the other hand, it has provided a great amount of information. The reorganization as well as validation of appropriate clinical cancer biomarkers, might results in the upcoming years by the utilization of bioinformatics and combined proteomic-based approaches. Large-scale illness screening is done by, a non-invasive option offered by means of highly sensitive technology through the initial screening of cancer samples, which can be validated by using antibody-based panels to identify possible markers for disease treatment, diagnosis as well as prognosis. For information translation and analysis, profound biochemical and biological information, as well as a powerful statistical parameter is essential. In cancer research to detect reliable biomarkers, bio-bank resources, proteomic-based technologies can be utilized together with developments in bioinformatics and data management systems.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Statement of informed consent was not applicable since the manuscript does not contain any patient data.

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