Chapter

Recognition of Multiomics-Based Molecule-Pattern Biomarker for Precise Prediction, Diagnosis, and Prognostic Assessment in Cancer

Xanquan Zhan, Tian Zhou, Tingting Cheng and Miaolong Lu

Abstract

Cancer is a complex whole-body chronic disease, is involved in multiple causes, multiple processes, and multiple consequences, which are associated with a series of molecular alterations in the different levels of genome, transcriptome, proteome, metabolome, and radiome, with between-molecule mutual interactions. Those molecule-panels are the important resources to recognize the reliable molecular pattern biomarkers for precise prediction, diagnosis, and prognostic assessment in cancer. Pattern recognition is an effective methodology to identify those molecule-panels. The rapid development of computation biology, systems biology, and multiomics is driving the development of pattern recognition to discover reliable molecular pattern biomarkers for cancer treatment. This book chapter addresses the concept of pattern recognition and pattern biomarkers, status of multiomics-based molecular patterns, and future perspective in prediction, diagnosis, and prognostic assessment of a cancer.

Keywords: cancer, multiomics, genomics, transcriptomics, proteomics, metabolomics, radiomics, molecule-pattern biomarker, pattern recognition

1. Introduction

Cancer is a leading cause of death worldwide, with increasing morbidity and mortality. Studies indicated that the number of new cancer case per year will be 19.3 million by 2025, and more than half of cancer cases and mortality occur in developing countries and the proportion tendency is estimated to increase by 2025 [1]. Cancer is a complex process involving multiple causes, multiple processes, and multiple consequences, which are associated with a series of molecular alterations in the different levels of genome, transcriptome, proteome, metabolome, and radiome, with between-molecule mutual interactions. Cancer arises when normal cells' orderly processes controlled multiplication and life span were interfered. It is also reported that person's genetic makeup and lifestyle factors such as diet, alcohol, smoke, and physical activity, influence the rate at which cancer develops and progresses.

Alterations or mutations of genetic substance of the cells are the main cause of changes in cellular behavior. Dysregulation of the normal cellular procedure in cancer for cell fission, differentiation, apoptosis and proliferation is due to alterations

in multiple genes expression and leading to an imbalance between cell replication and cell death, which is beneficial for growth of tumor cell population [2, 3]. With cancer progresses, the genetic drift of the cell population generates cell heterogeneity with characteristics involved in cell antigenicity, invasiveness, metastatic potential, rate of cell proliferation, differentiation state and response to chemotherapeutic agents [4–6]. A study showed that the mutation of two to eight driver genes is sufficient for an emblematical cancer occurrence. The passenger genes are not oncogenic and mutation of passenger genes is unable to cause occurrence of a cancer [7, 8]. Therefore, attention should be paid to a panel of genetic mutations, named gene pattern mutation. Depending on the genetic central dogma, gene pattern mutation may lead to a series of alterations of messenger RNA (mRNA) and protein expressions. With the use of this pattern, the condition of low sensitivity of a single-tumor marker or low specificity of a large number of samples is reduced when diagnosis models are set based on differentially expressed proteins or peptides between tumor tissues and normal tissues [9].

A cancer biomarker is defined as a substance or biological process that can indicate the presence of cancer in the body, which is important for people to monitor personal health [10]. Physical examinations (e.g., blood pressure), biological and genetic tests, along with others that can be objectively detected and used as indicators of pathogenic processes and alterations which may present as a result of treatment, are regarded as biomarkers [11, 12]. All the alterations in the levels of DNA, RNA, protein, and metabolite between cancer patients and healthy people could be called biomarkers, and therefore in terms of source, biomarkers usually are assorted into different categories including genetic biomarker, epigenetic biomarker, protein biomarker, metabolite biomarker and immunological biomarker and so on [13]. Generally, biomarkers used in clinic survey and diagnosis are from the four ways: (i) metabolites of tumor cells, (ii) abnormal differentiation of cellular gene products, (iii) tumor necrosis and exfoliation of tumor cells release into the blood circulation, and (iv) cell reactive products of tumor host cells [9]. Most of cancer biomarkers are detected in the tumor tissue or in blood. In order to maximize usefulness and minimize cost of screening or early detection, it is advantageous to be able to measure biomarkers in body fluid, which can be obtained using minimally invasive samples, such as blood, urine, sputum or stool [10]. Biomarkers play an important role in cancer for precise prediction, diagnosis and prognostic assessment. Thereby, with the development of biomarkers, they have far-reaching significances for people to recognize and treat cancer as follows: (i) the understanding of molecular mechanisms of diseases, (ii) identification of possible new disease pathways, (iii) prediction models of complex diseases, (iv) the determination of the level of biological activity of the disease, (v) refinement of disease phenotypes that may respond differently to specific treatments, (vi) the monitoring of treatment responses, and (vii) the potential application of precision medicine [14, 15]. However, it still remains a problem that biomarkers were detected after occurrence of cancer. With the fast development of image technology, radiomics is generated and can well solve that above problem. Quantitative analysis of imaging characteristics provides not only the tumor phenotype but also the underlying genotype information so that one can better diagnose and prognostic assessment for cancer patients [16]. A single tumor biomarker is insufficient and unreliable for precise prediction, diagnosis and prognostic assessment in cancer. The multi-parameter systematic strategies for predictive, preventive, and personalized medicine (PPPM) in cancer [4] emphasized that those molecule-panels, all of the differences and molecular alterations in the genome, transcriptome, proteome, metabolome, and radiome, with between-molecule mutual interactions, are the important resources to identify and recognize the reliable molecular pattern biomarkers for precise prediction, diagnosis, and

prognostic assessment in cancer. Pattern recognition is an effective methodology to identify those molecule-panels. In fact, pattern recognition means that recognize molecule-pattern biomarkers, in other words, to use a set of patterns that consist of several biomarkers to improve the accuracy and specificity of prediction, prevention, diagnosis, treatment, and prognostic assessment of tumor [9].

The rapid development of computation biology, systems biology, and multiomics is driving the development of pattern recognition to discover reliable molecular pattern biomarkers for cancer treatment. This book chapter addresses the concept of pattern recognition and pattern biomarkers, status of multiomics-based molecular patterns, and future perspective in prediction, diagnosis, and prognostic assessment of a cancer.

2. Pathophysiological basis of molecule-pattern biomarker in cancer

Cancer is a complex whole-body chronic disease, which results in a series of molecular alterations and associated with signal transduction system, cell cycle, proliferation, differentiation and apoptosis [17, 18]. Many factors are related to occurrence and development of a cancer.

Genomic instability plays a key role in cancer development and progression. It provides a way to make a cell or subset of cells gain an ability of selective advantage than adjacent cells, achieving outgrowth and advantages in the tissue microenvironment. Genomic instability can generate aneuploid cells. Aneuploidy influences on the transcriptome and proteome and further results in proteotoxic stress and activation of the endoplasmic reticulum stress response. Consequently, aneuploidy can regulate features of the cells and the microenvironment [19]. In normal cells, the quality of reproduction of the genome at each stage of the cell cycle is protected by checkpoints. The existence of aneuploid cells in cancer exactly suggested one or more checkpoints are failed. The genomic heterogeneity might provide growth advantages for cancer "tissue" under selection pressure, such as hypoxia, immunity, and treatment-related challenges [1]. Genomic instability in cancer causes a serious challenge for cancer treatment.

Genetic mutations that cause cell dysfunction in most of cases support the development and progression of cancer. Moreover, the interaction between cancer cells and their environment, known as the tumor microenvironment, and their mutually interacted regulatory factors, can affect disease initiation and progression. The tumor microenvironment is composed of stromal cells, extracellular matrix (ECM), and signaling molecules that communicate with cancer cells. The stromal cells including endothelial cells, pericytes, fibroblasts, and immune cells, along with the surrounding ECM, constitute a supporting matrix for the tumor and regulate the tumor microenvironment. Angiogenesis and metastasis, two pivotal hallmarks of cancer, are modulated by the composition of the tumor microenvironment. Furthermore, the tumor microenvironment is not only affected by signals from tumor cells, but also stromal components through influencing cancer cell function to promote tumor progression and metastasis [20, 21]. Therefore, tumor microenvironment also is an important aspect for cancer therapy.

Tumor heterogeneity is another momentous feature of malignant tumor and plays a vital role in development, progression, and treatment of cancer [22–26]. On the one hand, in most of cancer cases, heterogeneity is found that not only from same kind of tumor among different patients, but also in all tumor progression phases of the identical individual patients [27]. The genetic instability of tumor cell is tightly related to tumor progression and heterogeneity and leads to the presence of variations [28, 29]. On the other hand, tumor heterogeneity is relevant to the

individual differences between tumor patients. For example, the function of liver and kidney, age, physical condition, psychological status and personal lifestyle factors, are also another important factors which affect on the tumor progression and treatment [30]. A number of treatment plans of patients were designed according to the doctor's experiences and adopted same therapy model for different cancer patients in clinic. Due to ignore tumor heterogeneity, the "one-size-fits-all" therapeutic model resulted in the expected curative effect could not completely be achieved [4]. Thereby, tumor heterogeneity is becoming an important factor to hinder the effective treatment and cancer research.

Molecular mechanisms of initiation and progression of a cancer do not just exist one kind of intracellular signal pathway [31]. Several researches have indicated that phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK) and signal transducer, and activator of transcription 3 (STAT3) pathways were activated in obesity-associated colon cancer. Mammalian target of rapamycin (mTOR) as a down-stream of both PI3K/Akt and MAPK is highly activated [32]. Activated mTOR in proper order inhibits the PI3K/Akt pathway and further activates the STAT3 pathway [33]. In case that mTOR is inhibited, the activity of PI3K/Akt may obviously increase owing to the feedback inhibition of mTOR on PI3K activity [34]. Therefore, it is necessary to simultaneously suppress the expressions of mTOR and PI3K for the treatment of obesity-related cancer [4]. Hence one can see that the interaction and interrelationship of multiple signaling pathways is essential to pay more attention to study, and a single signaling molecule or biomarker is unreliable for the prediction, diagnosis, and treatment of cancer.

So far, there are many kinds of treatments for cancer including surgery, radiotherapy, and systemic treatments including cytotoxic chemotherapy, hormonal therapy, immunotherapy, and targeted therapies [35]. Personalized or individualized variations are related to human healthcare, and the relationship is shown (**Figure 1**). Three primary stages, prediction/prevention, early-stage diagnosis/early-stage therapy, and late-stage diagnosis/late-stage therapy are involved in human healthcare. Personalized or individualized variations can be used as biomarkers for prediction, and further the assessment of preventive response reflects the results of preventive treatments. Personalized or individualized variations also can be regarded as diagnostic biomarkers and further for cancer therapy. The assessment of therapeutic response, known as prognostic assessment, consists in early-stage therapy and late-stage therapy, and reveals the influence of therapeutic intervention. Of the three stages, prediction/prevention is the most significant part due to make people keep on a healthy condition and be treated in time once cancer occurs. Early-stage diagnosis/therapy also is better approach to block and repress the progression of cancer while the preventive strategy failed. Late-stage diagnosis/therapy is also named clinical diagnosis and treatment of a cancer. Unluckily, most of cancer cases were found in late stage. In order to avoid aforementioned problem and improve people's health level, many researchers concentrate on exploration of biomarkers on prediction/prevention and early-stage diagnosis/therapy for cancer [4]. According to functional classification, biomarkers are divided into two categories (**Table 1**): (i) serving for the mechanism and therapeutic targets, and (ii) devoting to prediction, diagnostic test, and prognosis assessment. The first kind of biomarkers is relevant to the initiation and development of disease, and directly indicates the mechanism and pathogenesis of the disease. Commonly, it is pivotal site in cell signal pathways, like P53 in nasopharyngeal carcinoma (NPC) [36]. Another kind of biomarkers does not need to be causal to the occurrence and development of the disease, but requires to be provided with specificity and a certain number of changes to be easily detected. Based on Bayes' rule, three or more key molecules can form molecule-pattern biomarker

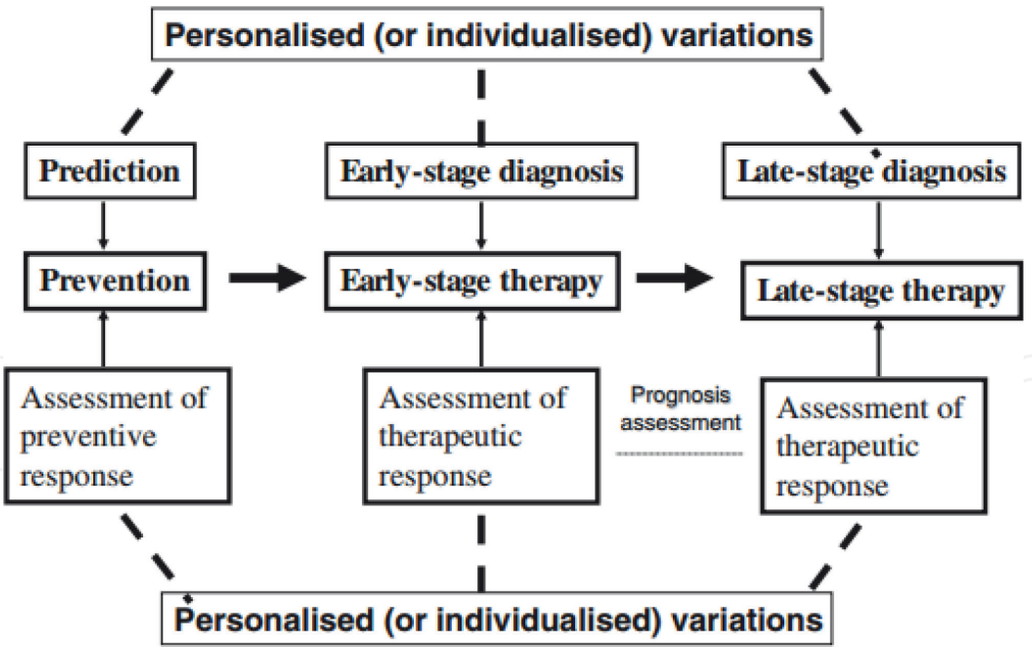

Figure 1.
Variations involved in each aspect of healthcare. Reproduced from Hu et al. [4], with permission from BioMed Central open access article, copyright 2013.

Types	Definition	Application
Type I	This type of biomarker exist a causal relationship with disease, associate with the initiation and development of disease, and can directly address the pathogenesis of disease.	Contribute to the mechanism and therapeutic targets of disease.
Type II	This type of biomarker does not need a causal relationship with the occurrence and development of disease, but requires specificity and a certain amount of change to be easily detected.	Contribute to the prediction, diagnosis, and prognostic assessment.

Table 1.
Concept and categories of biomarkers [9].

to improve the accuracy of cancer diagnosis and therapy [9, 37]. In summary, due to the complex pathophysiological basis of cancer, recognition of molecule-pattern biomarker for precise prediction, diagnosis, and prognostic assessment in cancer is an urgent demand to study and further close to realize precision medicine (PM) and PPPM.

3. Methodology of recognition of multiomics-based pattern biomarkers in cancer

Based on central dogma, genetic changes influence the RNA expression, and cause the alterations of proteins, along with taken into account the changes of metabolite and tumor heterogeneity, all above variations in genome, transcriptome, proteome, metabolome, and radiome are measured with corresponding omics methodology including genomics, transcriptomics, proteomics, metabolomics, and radiomics. Multiomics-generated biomarkers can make up integrative molecule-pattern biomarkers and pattern recognition for cancer treatment. This section mainly addresses the previous mentioned five omics approaches combined with computation biology and systems biology contribute to the development of cancer precise medicine (**Figure 2**) [9].

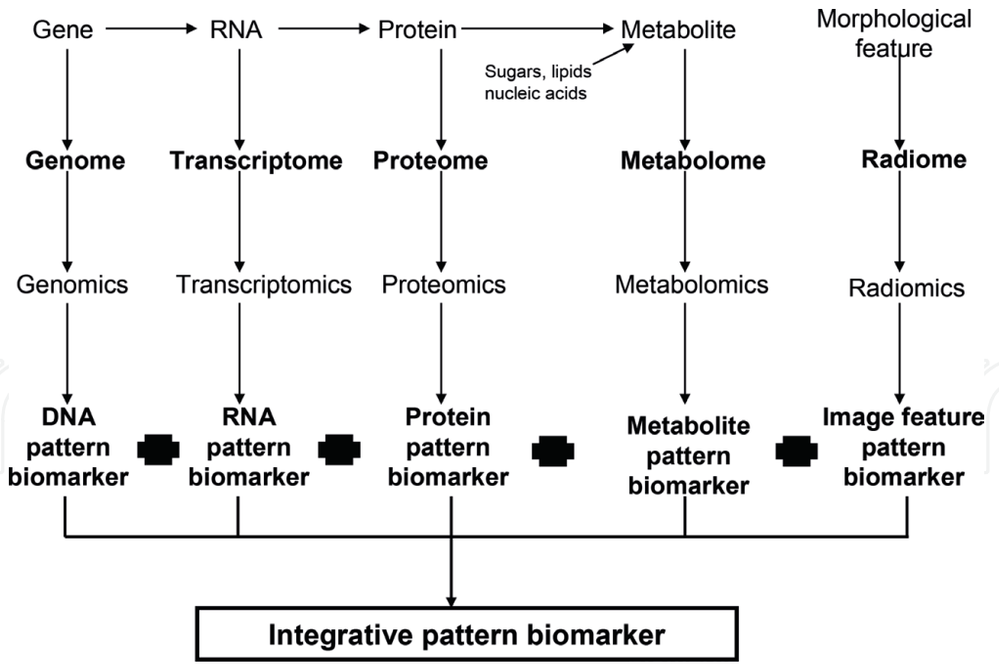

Figure 2.
Different levels of omics-based pattern biomarkers. Modified from Cheng and Zhan [9], with permission from Springer open access article, copyright 2017.

3.1 Genomics

The development of genomics drives the understanding and cognition of cancer. The development of gene sequencing technology is a significant advancement in the field of scientific research. First, based on the method of the previous "plus and minus," Sanger modified and invented the "dideoxy method" for DNA sequencing in 1977 [38–40]. Sanger sequencing acquired many achievements and completed a great work "Human Genome Project." Nevertheless, high cost and low throughput are disadvantages of Sanger sequencing technology [41, 42]. The limit of Sanger sequencing promotes the progression and generation of new sequencing technology. The second-generation sequencing technology has many advantages including higher speed and throughput, higher degree of parallelism, effective utilization of reagents and so on. However, problems still exist, such as the reduction of accuracy of sequencing and relatively higher cost [43, 44]. Due to the presence of shortcomings of the second-generation sequencing technology, the next-generation sequencing (NGS) requires to be discovered. The third-generation of sequencing technology is found to make up for the deficiency of second-generation. For example, PacBio RS and Oxford Nanopore sequencing not only possess fundamental character of the single molecule sequencing, do not need any polymerase chain reaction (PCR) process, availably avoid the PCR bias caused by the system error, and well improve the read length, but also keep the high-throughput and low cost of the second-generation technology [45]. Research demonstrates that accumulation of genomic alternations leads to the occurrence of cancer, which involves small insertions and deletions, base substitutions, copy number alterations (CNA), chromosomal rearrangements, and microbial infections [46]. Besides, a number of polymorphic CNAs have been discovered in the human genome [47]. DNA microarrays, also named as "gene chip" or "DNA chip," obtained a great success that could monitor tens of thousands of one time expression and hundreds of thousands of genes. Single nucleotide polymorphisms (SNPs) are the most common form of DNA variation in the human genome, approximately occurring one time every 100–300 bases [48]. Many studies suggested SNPs might affect the activity

of metabolism-related key enzyme, therefore generating effects on tumor progression and drug efficacy. However, with in-depth research, scientists indicated one SNP or a simple CNA could not influence the whole development of the individual process of cancer. The occurrence of a cancer is a result of changes of multiple sites, thus current study is shifting towards several genetic mutation patterns [9]. In addition, breakthrough progress has been made in strategies for obtaining DNA information of tumor tissues. Currently, a novel method found to collect DNA information of tumor tissue is called circulating tumor cell (CTC), which is a general term for all tumor cells in peripheral blood [49]. Compared to tumor tissue samples, blood specimens possess more advantages such as less invasive, easy to acquire, and can be collected repeatedly. It is a typical source of specimens and convenient to operate in clinical practice, so that significantly improves the value of aforementioned method [9]. Circulating tumor DNA (ctDNA) means a tumor cell body that is apoptotic by shedding or released into the circulatory system, and rapid development of gene sequencing results in that it is able to detect in the blood [50]. Therefore, ctDNAs are possible to find key mutation sites and served as biomarkers. Over the past few years, liquid biopsy combined with ctDNA analysis is helpful and beneficial for the molecular diagnosis and monitoring of cancer. Moreover, BEAMing (emulsion, amplification, beads, and magnetics) and CAPP-seq (cancer personalized profiling by deep sequencing) are discovered and used to quantify ctDNA in blood [51, 52]. Furthermore, there are several unknown things about ctDNA including its size, existing form, mechanisms of released into blood stream, and its degradation rate in blood [53]. In summary, the development of genomics provides the method, important information about genome, and impactful biomarkers for diagnosis of cancer and drives the progress of cancer genomics.

3.2 Transcriptomics

Based on the genetic central rule, DNA through self-replication and transcripts to form the mRNAs, and finally translates to be a protein. The mRNA is served as a bridge between gene and protein in biological process and linked genome and phenotype. Once variation of gene sequence of mRNA occurs, the amino acid sequence of the protein will be correspondingly altered. Therefore, the understanding of transcriptomics is important for addressing functional elements of the genome and cognizing the development of cancer. The key goal of transcriptomics is to classify all types of transcripts, reveal the transcriptional structure of the genes, and quantify the expression levels of each transcript during development and under different conditions. Nowadays, many methods are generated to be used for the study of transcriptome, such as hybridization-or sequence-based approaches [54]. In general, the way of nucleic acids with hybridization-based is incubation of fluorescently labeled-complementary DNA (cDNA) from reverse transcription of different mRNAs with a microarray contained genes of interest, then digitized with a dedicated scanner and image analysis and finally gene name, clone identifier, and intensity values are acquired [55]. Furthermore, genomic tiling microarrays are found to provide a more unerring opinion of the transcriptional activities within a genome [56]. Howbeit, there are some disadvantages, like relying on the current knowledge of genome sequence, high background levels owing to cross-hybridization, and both background and saturation of signals resulted in a limited dynamic range of detection [57, 58]. Sequence-based strategy is able to detect cDNA sequence but not depend on the probes. With the development of high-throughput DNA sequencing technique of NGS, a new method used for mapping and quantifying transcriptome is occurred, named RNA-seq. It possesses a lot of advantages, for instance, high throughput, high sensitivity, high resolution, and no reconstructions. RNA-seq is able to analyze

the whole transcriptome of any species, including detection of unknown genes or transcripts, exact identification of the cleavage site, and a variable SNP or untranslated region (UTR region) [16]. In another hand, the research field of noncoding RNA (ncRNA) should be paid more attention. The ncRNAs consist of tRNA, rRNA, snoRNA, snRNA, piRNA, miRNA, and lncRNA [59]. Of them, miRNA and lncRNA are familiar and studied more. MicroRNAs, with a sequence of approximately 21 bp, are a kind of small ncRNAs, which take part in multiple cellular functions including proliferation, differentiation, metabolism and apoptosis [60]. In general, TaqMan-based real-time quantitative PCR (RT-qPCR) with separate microRNA-specific primers and probes is used to detect the expression levels of microRNAs. The expression of microRNAs is frequently dysregulated in a cancer-specific manner so that microRNAs are potential to be biomarkers for cancer detection. Many studies demonstrated the microRNAs as biomarkers for prediction, diagnosis, and prognosis for cancer [9]. However, current studies on the function of miRNAs have not yet been fully understood, previous studies of miRNAs have found different types of miRNAs and their effects on oncogenesis and gene expression level of miRNA as antioncogene. In addition, it is predicted that about 30% of protein-encoding genes are regulated by miRNAs [61, 62]. lncRNAs execute multiple functions in cells and are reported as biomarkers in many types of cancers, like breast, lung, gastric, liver, and prostate cancers [63]. The lncRNAs play a vital role in recognition and treatment of cancer. Up to now, the biological effects of lncRNAs are still incompletely clear, but they have already been found to be prolific regulators of many cell processes. Several lncRNAs overlap with gene promoters, thus transcription of these lncRNAs might interfere with nucleosome-deleted regions and histone modifications of nucleosomes in those promoters [64, 65]. Moreover, detection of lncRNA is easily influenced by anticoagulant such as EDTA, and lncRNA is lightly degraded by other substance of the blood so that it cannot be preserved for a long time. More researches are necessary to solve these problems in the future [9].

3.3 Proteomics

Proteins are most direct phenotype characteristics of DNA in biological system. Proteins are related to multiple cellular mechanisms including cell motility, cell growth, cell signaling, and protein metabolic process [66]. The study of proteome is beneficial to the understanding of cancer. The aim of proteomics is to identify proteins and construct protein pathways and networks to characterize information and ultimately understand the functional relevance of proteins in cells or organisms [67]. The proteome is one of the most complex omes among genome, transcriptome, and proteome. The amount of human proteins and their variants or protein species are approximately reached to billions [4]. Furthermore, one gene is corresponded to multiple proteins, known as one gene-multiple proteins model, not one gene-one protein model so that the complexity of proteome is conceivable [68, 69]. So far, only the sequence and copy number of DNAs and RNAs in a genome are able to measure with current technologies. However, a lot of information can be acquired in a proteome, including amino acid sequence, copy number, splicing, variants, post-translational modifications (PTMs), spatial conformation, and spatial redistribution [16]. Proteomics mainly applies to the detection, identification, and quantification of the protein in a defined system (cell, tissue, organ, and organelles). Of detection technologies, gel and gel-free methods are used [68, 69]. Two-dimensional gel electrophoresis (2DGE), two-dimensional difference in gel electrophoresis (2D DIGE), and one-dimensional gel electrophoresis (1DGE) are mainly involved in gel-based methods [69, 70]. When ones want to detect a certain variants of a given protein or a kind of PTM with gel-based methods, a specific antibody is

necessary to be used [70–72]. Gel-free methods primarily have hydrophobic interaction chromatography (HIC) to separate large bio-molecules, like proteins, C4 or C5 reverse phase liquid chromatography (RPLC) with 300 Å pore-size particles, capillary electrophoresis (CE)-electrospray ionization-mass spectrometry (CE-ESI-MS), multiplexed gel-eluted liquid fraction entrapment electrophoresis (mGELFrEE; size-based separation) with 8 parallel glass gel column, and weak-cation exchange chromatography (WCX) in combination with HIC in a single column with a single phase (2D-LC; from WCX to HIC mode) [73–80]. Mass spectrometry (MS) plays an important role in identification of protein variants and PTMs, because the amino acid sequence of complete proteins, splicing sites and PTM-sites are able to be determined with MS [69, 71, 81, 82]. Tandem mass spectrometry (MS/MS) can detect amino acid sequence of a protein, and directly authenticate the errors of amino acid sequence, variations, and modifications, which causes character of PTMs and protein variants with different types of mass spectrometers, for instance, matrix-assisted laser desorption ionization-time of flight-time of flight (MALDI-TOF-TOF), LTQ Orbitrap system, triple TOF 5600 or 6600 systems and Fourier transform ion cyclotron resonance (FTICR) with different types of ion fragmentation models including electron capture dissociation (ECD), electron transfer dissociation (ETD) and collision induced dissociation (CID). Different types of samples and research objectives should use identification techniques that are appropriate for them [80]. Quantification of protein is necessary to clarify their biological significance, which is detected with three main methods, including 2DGE-based quantitative methods, label-free quantitative techniques like sequential window acquisition of all theoretical mass spectra (SWATH) and selected/multiple reaction monitoring (SRM/MRM), and stable isotope-labeled quantitative approaches including isobaric tags for relative and absolute quantification iTRAQ [80]. Furthermore, combined with structural proteomics maybe is better for understanding the biological functions in biological systems [83, 84]. Also, the study of the protein-protein interaction analysis and cell signal pathways has become a hot topic. The identification of protein-protein interactions is meaningful for understanding signal transduction mechanisms and establishing intracellular signaling networks [4]. Under pathological conditions, the body can secrete several special proteins owing to the other mRNA synthesis and alternative chromosomal genetic variations involved cancer, diabetes and Alzheimer disease [85]. Therefore, protein is able to be a biomarker and proteomics is an important strategy for the study of cancer.

3.4 Metabolomics

Metabolites and proteins are equally important to understand cancer. Metabolites are small molecules (<1 KDa) produced by metabolism, which can provide functional information that is not directly available from the genome and proteome in cellular and tissue states [86, 87]. Metabolites are derived from lipids, sugars, proteins, and nucleic acids in a given biological system, cell, tissue, or body-fluid [88–90]. The alteration in metabolites is relevant to multiple factors, such as genetic, environment, internal, external, drug, and dietary factors. These metabolic profiles are related to the whole biochemical processes that are the starting, intermediate or final products and provide complex interactions information between the genes and the environment of a given condition [91, 92]. Metabolites may be capable of reflecting physiological and pathological processes and monitoring the progression of a disease, and are helpful to predict, diagnose, and treat [93]. Therefore, metabolomics is a methodology used to study metabolome, refers to identification of biochemical and molecular features of metabolome, among different metabolite interactions between genetic/environmental factors and metabolites, and to

assessment of biochemical mechanisms associated with a given conditions like different pathophysiological processes [94]. Generally, two strategies, targeted and untargeted methods, are mainly employed to detect variations in a metabolome [95, 96]. Targeted metabolomics method concentrates on quantification of the variations of the hypothesis-driven known metabolite profiling (like metabolites that are produced from one or more unknown pathways) between or among groups, followed by multivariate statistical analysis and establishment of mathematical model [95, 97]. Up to now, the familiar techniques used for targeted metabolomics are the triple quadrupole mass spectrometry (QqQ-MS) in the SRM/MRM modes with optimized sample extraction and liquid chromatography-mass spectrometry (LC-MS) conditions [98, 99]. The untargeted metabolomics is different from targeted method, which shows in these aspects, such as no hypothesis-driven strategy, and the whole comprehensive study variations of metabolome in a biological system without bias for exploration of metabolite biomarkers for impactful prediction, diagnosis, and prognostic assessment [80, 96]. The current techniques used to qualify and quantify the metabolomic variations are nuclear magnetic resonance (NMR)-based methods and mass spectrometry (MS)-based methods [88, 100–102]. NMR-based methods involve one-dimensional NMR (1D-NMR), two-dimensional NMR (2D-NMR), and three-dimensional NMR (3D-NMR). The way to provide chemical structural and molecular environment information is utilizing the interaction of spin active nuclei (^{13}C, ^{1}H, ^{31}P, ^{19}F) with electromagnetic fields [100, 101]. NMR-based methods possess many advantages, including nondestruction of sample, minimal sample preparation, high reproducibility, relative high throughput, availability of databases, and availability of molecular dynamic and compartmental information with diffusional methods. However, overlapping of metabolites, low sensitivity, and high instrumentation cost are its disadvantages [103]. MS-based methods include direct injection coupled with MS (DIMS), LC-MS, gas chromatography coupled with MS (GC-MS), capillary electrophoresis coupled with MS (CE-MS), and ion mobility coupled with MS (IM-MS) [80]. Aforementioned five MS-based methods have its advantages and limitations, and proper combination helps ones to better study. In clinic, in order to measure variations in a metabolome, the biological samples are extremely complex, including cell, tissue extracts and body-fluid. Serum/plasma and urine are commonly used body-fluid for metabolomics analysis in all diseases because they are very easily acquired and prepared, and almost no injury for patients [88, 104, 105]. Additionally, many researches have reported that cerebrospinal fluid (CSF), saliva, exhaled air, tears, and synovial fluid are likely to be regarded as biomarkers for a specific disease [80]. Metabolites are important source of biomarkers, and metabolomics methods reasonably adopted are beneficial to predict, diagnose, and evaluate for cancer.

3.5 Radiomics

Medical imaging technologies, including computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI), are vital to diagnose and check after treatment for cancer. Medical images provide ones with a number of information about tumors, which include location and volume of tumor, probable measurements of diameter, the overall and marginal morphology of the lesion, the relationship with surrounding tissues, internal heterogeneity, CT and PET/CT values, MRI signal height and other values. This information is instructive for the diagnosis of tumors and the decision-making of clinical treatment. However, it is not able to accurately reflect the morphological and behavioral complexities of a tumor, with limitation in the assessment of treatment sensitivity and prognosis [106]. With the rapid development of technology, emerging discipline- radiomics

has occurred. Based on excellent computer technology and advanced statistical methods, radiomics achieves high-throughput extraction and conversion of quantitative features of medical data, and make it serve for clinic decision of cancer [16]. Radiomics has enabled medical imaging to achieve a qualitative to quantitative transition and provides guidance for clinical treatment, and a large amount of data has the potential to develop into biomarkers that contribute to further research in cancer.

4. Application of pattern biomarker for PPPM or PM in cancer

Based on the development of multiomics technology, a series of molecular alterations in the levels of genome, transcriptome, proteome, metabolome, and radiome are possible to be detected and measured, which also offer many kinds of potential biomarkers to ones and are beneficial to well understand and study for cancer. In order to improve the treatment effect and approach PPPM or PM in cancer, the methodology of recognition of multiomics-based molecule-pattern biomarker is presented. The concept "pattern biomarker" refers to several biomarkers make up a pattern for precise prediction, diagnosis, and prognostic assessment in cancer, which can be derived from genome, transcriptome, proteome, metabolome, or radiome, and each pattern biomarker is able to be used as a biomarker for recognition, therapy, and other-related research of cancer. Many researches prove that the use of more biomarkers can increase the accuracy of understanding for cancer. For instance, based on somatic cell gene copy number aberrations, the alterations of gene expression analyzed with genomic and transcriptomic data and long-term clinical outcomes indicated several potentially important targeted therapeutic response-related events and mentioned a novel molecular classification of breast cancer patients [107]. Genomic combined with proteomic data analysis revealed that PI3K pathway aberrations are popular in hormone receptor-positive breast cancer, which provides new idea for clinically targeted therapy [108]. Tissue transcriptomics and urine metabolomics integrated analysis identified four urinary biomarkers that are more reliable compared to biomarkers derived from single omics

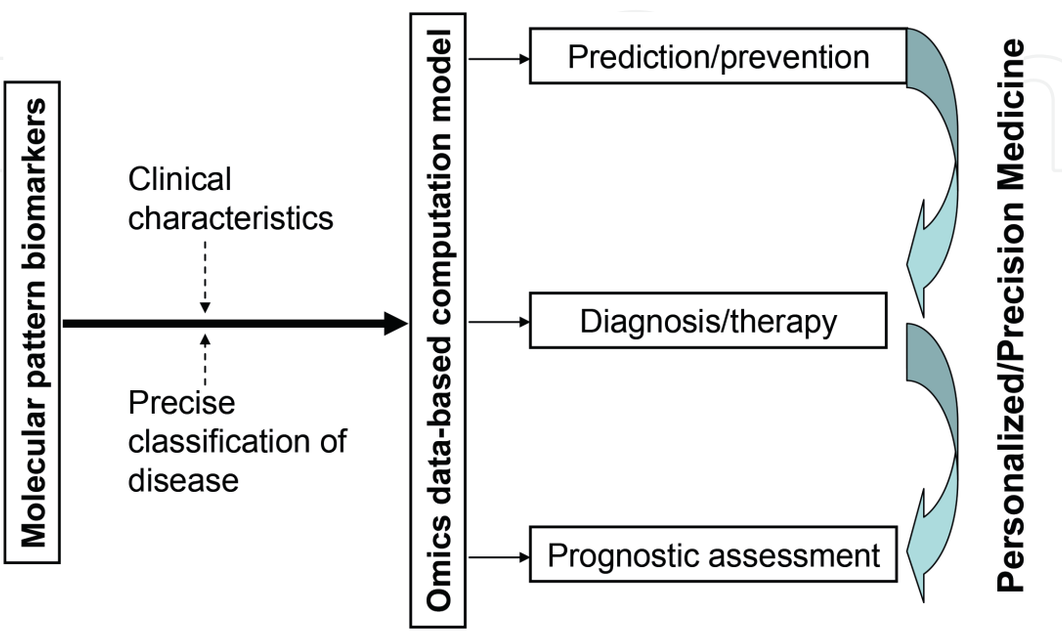

Figure 3.
Application of pattern biomarker in personalized medicine or precision medicine.

[109]. Comprehensive analysis of transcriptomic and proteomic data suggested a highly significant enrichment of gonadotropin-releasing hormone (GnRH) signaling pathway that was not deciphered with single omics dataset in glioblastomas, which proved the necessity of multiomics research [110]. In addition, the failure of sorafenib-treated HCCs was employed with an integrated quantitative proteomics and phosphoproteomics analysis, and found that the targeted drug can effectively inhibit its target kinase in Raf-Erk-Rsk pathway, but the downstream targets of Rsk-2 (eIF4B, filamin-A, and so on) were not affected, suggesting that they may be replaced by another active pathway and lead to treatment failure [111]. However, there are also many challenges needed to be faced. Considering the tumor heterogeneity, individual difference, different stages of tumor development, the recurrence of tumor, and so on, one designs an ideal model for prediction, prognosis, and prognostic assessment of cancer in order to further realize PPPM or PM (**Figure 3**).

5. Conclusion

Cancer is a complex whole-body chronic disease, is involved in multiple causes, multiple processes, and multiple consequences. On the contrary, the complexity of cancer exactly provides ones with more opportunities for PPPM or PM in cancer. The rapid development of genomics, transcriptomics, proteomics, metabolomics, and radiomics in combination with advanced computation biology and systems biology drives the development of pattern recognition to find reliable and effective molecular pattern biomarkers for cancer treatment, and further achieves PPPM or PM. Multiomics integration analysis is beneficial to better understand cell malignant transformation and tumor progression, clarify molecular mechanisms of a cancer, discover novel biomarkers and targeted drugs, and improve the effect of targeted therapies.

Acknowledgements

The authors acknowledge the financial supports from the Xiangya Hospital Funds for Talent Introduction (to X.Z.), the Hunan Provincial "Hundred Talent Plan" program (to X.Z.), the National Natural Science Foundation of China (Grant No. 81572278 and 81272798 to X.Z.), China "863" Plan Project (Grant No. 2014AA020610-1 to X.Z.), and the Hunan Provincial Natural Science Foundation of China (Grant No. 14JJ7008 to X.Z.).

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations.

Author's contributions

Z.T. analyzed references and wrote manuscript draft of the book chapter. C.T. M.L. participated in collection of references and analysis of data. X.Z. conceived the concept, designed the book chapter, and critically revised/wrote the book chapter, coordinated and was responsible for the correspondence work and financial support.

Acronyms and abbreviations

CAPP-seq	cancer personalized profiling by deep sequencing
cDNA	complementary DNA
CE	capillary electrophoresis
CE-MS	capillary electrophoresis coupled with MS
CE-ESI-MS	capillary electrophoresis-electrospray ionization-massspectrometry
CID	collision induced dissociation
CNA	copy number alterations
CSF	cerebrospinal fluid
CT	computed tomography
CTC	circulating tumor cell
ctDNA	circulating tumor DNA
DIMS	direct injection coupled with MS
ECM	extracellular matrix
ECD	electron capture dissociation
ETD	electron transfer dissociation
FTICR	Fourier transform ion cyclotron resonance
GC-MS	gas chromatography coupled with MS
GnRH	gonadotropin-releasing hormone
HIC	hydrophobic interaction chromatography
lncRNAs	long noncoding RNAs
IM-MS	ion mobility coupled with MS
iTRAQ	isobaric tags for relative and absolute quantification
LC-MS	liquid chromatography-mass spectrometry
MAPK	mitogen-activated protein kinase
mGELFrEE	multiplexed gel-eluted liquid fraction entrapment electrophoresis
mRNA	messenger RNA
MS	mass spectrometry
MALDI-TOF-TOF	matrix-assisted laser desorption ionization-time of flight-time of flight
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
ncRNA	noncoding RNA
NGS	next-generation sequencing
NMR	nuclear magnetic resonance
NPC	nasopharyngeal carcinoma
1DGE	one-dimensional gel electrophoresis
PCR	polymerase chain reaction
PET	positron emission tomography
PM	precision medicine
PPPM	predictive, preventive, and personalized medicine
PI3K/Akt	phosphoinositide 3-kinase/protein kinase B
PTMs	post-translational modifications
QqQ-MS	quadrupole mass spectrometry
RPLC	reverse phase liquid chromatography
RT-qPCR	real-time quantitative PCR
SNPs	single nucleotide polymorphisms
STAT3	signal transducer, and activator of transcription 3
SWATH	sequential window acquisition of all theoretical mass spectra

SRM/MRM	selected/multiple reaction monitoring
1D-NMR	one-dimensional NMR
2D-NMR	two-dimensional NMR
3D-NMR	three-dimensional NMR
2DGE	two-dimensional gel electrophoresis
2D DIGE	two-dimensional difference in gel electrophoresis
MS/MS	Tandem mass spectrometry
UTR region	untranslated region
WCX	weak-cation exchange chromatography

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