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Review

Clinical multi-omics strategies for the effective cancer management

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ABSTRACT

Cancer is a global health issue as a multi-factorial complex disease, and early detection and novel therapeutic strategies are required for more effective cancer management. With the development of systemic analytical -omics strategies, the therapeutic approach and study of the molecular mechanisms of carcinogenesis and cancer progression have moved from hypothesis-driven targeted investigations to data-driven untargeted investigations focusing on the integrated diagnosis, treatment, and prevention of cancer in individual patients. Predictive, preventive, and personalized medicine (PPPM) is a promising new approach to reduce the burden of cancer and facilitate more accurate prognosis, diagnosis, as well as effective treatment. Here we review the fundamentals of, and new developments in, -omics technologies, together with the key role of a variety of practical -omics strategies in PPPM for cancer treatment and diagnosis.

Biological significance: In this review, a comprehensive and critical overview of the systematic strategy for predictive, preventive, and personalized medicine (PPPM) for cancer disease was described in a view of cancer prognostic prediction, diagnostics, and prevention as well as cancer therapy and drug responses. We have discussed multi-dimensional data obtained from various resources and integration of multisciplinary –omics strategies with computational method which could contribute the more effective PPPM for cancer. This review has provided the novel insights of the current applications of each and combined -omics technologies, which showed their powerful potential for the establishment of PPPM for cancer

1. Introduction

Cancer is the second leading cause of death and remains a major public health problem [1]. Cancer is a heterogeneous disease involving the complex interplay of various internal and environmental factors [2], which results in individual alterations of DNA, RNA, proteins, metabolites, and molecular networks. Alterations in the expression and interaction of multiple molecules lead to dysregulation of cellular programs, which favors cancer cell growth and leads to genetic drift in the cell population.

In general, cancer is treated in the primary setting, which is informed largely by clinicopathological factors and histopathology with limited molecular testing. Current cancer treatment is based on general parameters such as tumor stage and/or tumor grade, which primarily consider tumor size, extent of primary tumor spread, the amount of abnormality, and/or expression of prognostic and predictive biomarkers. There are different levels of evidence-based knowledge and experience generated by epidemiological and clinical studies or evidence-based medicine. However, large randomized studies have determined approaches for a population, but not for individuals. This very limited molecular testing requires much effort in cancer research and practice to enhance our understanding of cancer hallmarks or phenotypes that contribute to tumorigenic behavior [3]. The translation of knowledge of cancer biology into clinical practice remains challenging, and therapeutic and diagnostic/prognostic models of cancer have resulted in a paradigm shift from traditional single-factor strategies to multi-parameter systematic strategies (e.g., from radiotherapy and chemotherapy to personalized strategies) in cancer research and treatment. The development of predictive, preventive, and personalized medicine (PPPM) is expected to facilitate more-accurate prediction of treatment responses, stratification of patient groups, and personalization of medicine [4].

The development of -omics strategies (genomics, transcriptomics, proteomics, and metabolomics), together with the rapid evolution of data technologies, has improved our understanding of tumor biology and clinical management of cancer. -Omics approaches have revealed

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key mutations and molecular pathways, and identified and quantified differentially expressed molecules, independently of trigger factors, which has led to the identification of a large number of potential targets. Multi-dimensional -omics data that are systematically characterized in individuals by computational analysis using bioinformatics approaches enables identification of drug targets and the optimal treatments. Genomics deals with genome infrastructure and function by DNA sequencing and genetic polymorphism analysis. A systemic genomic approach using next-generation sequencing (NGS) technologies can elucidate genotype-phenotype associations compared with analyses using only a single data type. Completion of the Human Genome Project has enhanced our understanding of cancer, in particular the role of DNA mutations in different types of cancer, and aided in the development and prediction of the efficacy of novel therapeutics. Transcriptomics is the study of the transcriptome, which is the precursor of the proteome, the entire set of proteins expressed by a genome. Expression profiling of mRNAs with recent advances in RNA interference (RNAi) screening and RNA sequencing (RNA-seq; also known as whole transcriptome shotgun sequencing, WTSS) using NGS technologies has resulted in the discovery of predictive biomarkers.

Genomics is simple and relatively rapid, and serves as a starting point for other clinical -omics strategies. Discovery and information of sequences is helpful for PPPM, but does not provide functional information, such as post-translational modifications (PTMs). Thus, investigation and development of proteome-based biomarker discovery is also important. Proteins carry out most biological processes and dynamic variations in protein expression and PTMs reflect disease activity and status, which are systematically characterized in individual cancer patients and analyzed using bioinformatics approaches [5]. Although information on protein pathways and network information flow within a cell is useful, the level of proteomic variation involved in the regulation of biological functions is considerable and dynamic. The metabolome is another valuable resource for detecting unknown compounds and alterations in cancer patients, because it is the final downstream product and the most predictive marker of phenotypes in PPPM. In addition to genomics, proteomics, and metabolomics, other regulatory information, such as the transcriptome and epigenome, is of importance in cancer PPPM. No method of simultaneously assaying the entire genome, transcriptome, proteome, and metabolome has been developed; therefore, systematic multi-omics strategies with integrated data systems are required for PPPM for cancer. Here, we review multiparameter strategies to predict, prevent, and treat cancer.

2. PPPM in cancer

PPPM for cancer is a global issue. The concept of PPPM was addressed at the first European Association for Predictive, Preventive and Personalized Medicine (EPMA) World Congress, in 2011 [6], and global collaboration is contributing to the development and implementation of innovative PPPM strategies. The United States has established a PPPM policy [7,8] and EPMA has released a long-term strategy for the promotion of PPPM [6,9,10]. Efforts to develop PPPM strategies involve use of a variety of novel, rapid, sensitive, and specific methods to establish optimal cancer treatment strategies for individual patients [11].

PPPM trials aim to provide rapid, efficient, and accurate prediction of the most appropriate course of action for a patient. For example, the precision medicine initiative trials, NCI-Molecular Profiling-Based Assignment of Cancer Therapy (MPACT) and NCI-Molecular Analysis for Therapy Choice (MATCH), have established the appropriate treatments for various cancer types according to genetic alterations using NGS technology [12]. The Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) and IMPACT2 studies of metastatic cancer are also underway [13].

The challenge of PPPM for cancer is to reduce the gap between research scientists and clinicians. Thus, efforts to identify the optimal PPPM for cancer patients will require identification of the appropriate dose and time of administration of the optimal medication for the individual patient [11]. New advanced breast cancer patient stratification and new paradigm of so-called “pre-metastatic niches” were addressed for the effective breast cancer management [14,15] and pretreatment prediction of chemoradiotherapy response was also described in rectal cancer in a view of PPPM [16]. In addition to cancer, other diseases such as wound healing were considered in PPPM by multi-professional strategies with various risk factors [17].

2.1. Biomarker resources

PPPM relies on identification and validation of biological markers of cellular, biochemical, or molecular alterations of tissues, cells, or fluids. Recent developments in -omics technologies have led to the investigation of various biological samples for prognostic and diagnostic biomarkers of cancer. Discovery of biomarkers has contributed to cancer research and drug development to identify mechanisms of cancer progression, enhance individual and group risk assessments, establish drug-responses, and reduce bias in the measurement of cancer risk factors. A number of biomarkers have been identified in biological samples, including tissue, blood, and urine. These resources have advantages and disadvantages for research and clinical use (Table 1), and several points, including storage conditions, must be considered for sample management. Biobanks or biorepositories maintain and store biological samples, together with clinicopathological and medical history information. Well-regulated population- and disease-based biobanks containing various biological materials serve as an excellent resource for cohort studies as well as investigations of a particular disease. Such studies aim to establish novel and reliable PPPM strategies for treatment, prediction, and diagnosis of disease, as well as monitoring patient responses to treatment [11,18].

2.1.1. Tumor tissue

Tumor tissue, which can be routinely obtained from surgical specimens or biopsies, is a useful resource for the discovery of biomarkers. Fresh, frozen, and formalin-fixed paraffin-embedded (FFPE) tissues have provided valuable information for clinical diagnosis and treatment using genomics, transcriptomics, proteomics, and metabolomics approaches. Recently NGS-based genomics and mass spectrometry (MS)-based proteomics have been applied to FFPE clinical specimens. Tissue biopsy is the gold standard for most cancers, and enables direct analysis, but challenges due to sampling error—including surgical complications, tumor dissemination, false negative results, and its invasiveness—remain to be overcome [19].

Table 1
Materials used for the identification of cancer biomarkers.

Resources	Advantages	Disadvantages
Blood	• Minimally invasive • Less expensive • Relatively accurate • Repeated at shorter intervals	• Complex • Patient variability • Shipment
Tissue	• Direct analysis	• Highly invasive • High cost • Sampling error
Urine	• Non-invasive • Sufficient volume • Less expensive • Known testing accuracy	• Low concentration of molecules • Patient variability • Ease of dilution with others
Semen	• Relatively non-invasive • Large volume • Low coast	• Low concentration of molecules • Patient variability
Saliva	• Simple • Non-invasive • Minimal processing	• Interfering substances • Technical challenge