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Advancing cancer diagnosis and treatment: Integrating molecular biomarkers and emerging technologies.

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ABSTRACT

Cancer biomarkers can be derived from tumor cells or neighboring cells within the tumor microenvironment. Over the past few decades, various molecular markers, including DNA (mutations, copy number variations), RNA (mRNA, microRNA, circular RNA), proteins, and metabolites, have been identified with the aid of rapidly evolving technologies. Some of these markers have demonstrated potential clinical utility, while others have provided new insights into the deregulation of normal molecular and cellular processes that lead to tumorigenesis. Publications in this special issue of the *Biomedical Journal* introduce contemporary approaches aimed at enhancing cancer diagnosis, and monitoring of cancer and treatment options, with the ultimate goal of reducing mortality. These studies highlight the importance of integrating advanced technologies with clinical strategies for treatment of cancer.

Cancer is a complex and heterogeneous disease influenced by multiple factors including genetic, epigenetic, and environmental factors. Advances in the identification of cancer molecular biomarkers have provided significant opportunities to deepen our understanding of cancer biology. These biomarkers have also emerged as critical tools for cancer diagnosis, prognosis, and predicting therapeutic response. Key technologies such as genomics, transcriptomics, proteomics, epigenomics, and more play a pivotal role in biomarker discovery. The measurable or quantitative nature of these biomarkers makes them essential indicators for precision medicine. As illustrated in Graphic Abstract, we briefly provide a summary of various types of biomarkers associated with cancer in six publications in this special issue.

MicroRNAs (miRNAs) have emerged as promising non-invasive biomarkers for colorectal cancer (CRC). Their stability in stool samples and association with CRC make them valuable for early diagnosis and monitoring. Chen and Chang analyzed fecal miRNA profiles from published studies to investigate the potential utility of fecal miRNA for CRC diagnosis [1]. Through a thorough literature review and rigorous selection process, the authors proposed a dataset comprising eight high-throughput profiling studies for further analysis. The differentially expressed miRNAs across these datasets were compared; however, there was minimal overlap, highlighting the complexity of miRNA expression in CRC. Despite these challenges, the potential of fecal miRNAs in CRC screening is significant. Their non-invasive nature and ability to reflect the gastrointestinal environment make them attractive candidates for early detection and monitoring of CRC, as well as other gastrointestinal diseases. While fecal miRNAs hold promises as non-invasive biomarkers for CRC, further clinical validation is essential to establish their utility in routine screening and diagnosis.

Liquid biopsies, which analyze circulating tumor cells (CTCs) and cell-free DNA (cfDNA) in blood samples, have significantly advanced cancer diagnostics and monitoring. CTCs are intact cancer cells shed from primary or metastatic tumors into the bloodstream, while the cfDNA refers to fragmented DNA released into the bloodstream, primarily from apoptotic and necrotic cells. Two publications by Wong et al. and Chiang et al. have addressed the methodologies used for CTCs or cfDNA detection in blood samples, which serves as indicators of the metastatic potential in cancer patients [2,3]. Wong et al. discussed methods applied to detect epigenetically altered cfDNA. These modifications include DNA methylation, DNA fragmentation patterns, and histone modifications, which play a pivotal role in the regulation of gene expression and genomic stability in cancer cells [2]. Chiang et al., on the other hand, have evaluated the potential role of CTCs in real-time tracing of tumor recurrence and distant metastasis of cancers [3]. Prospectively, they applied a simplified *ex vivo* culture protocol to expand the CTCs across 8 different cancer types. They showed that the CTC growth rate correlated with patient status-disease progression, and thereby could guide cancer treatment. Thus, combining measurements of CTCs and cfDNA could potentially enhance the sensitivity and specificity of liquid biopsies in cancer management.

Mitochondria, beyond serving as the powerhouse of the cell, play a pivotal role in tumorigenesis. Al -Faze et al. describes the essential functions of mitochondria in the growth, metastasis, and carcinogenesis of cancer cells, with a focus on their metabolic effects [4]. Metabolic reprogramming, a hallmark of cancer cells, ensures a continuous supply of proteins, nucleotides, and lipids necessary for rapid proliferation and tumor development. Alterations in mitochondrial function, including mutations in mitochondrial DNA (mtDNA), excessive production of reactive oxygen species (ROS), mitochondrial damage, and calcium excess, play a crucial role in caner progression. In ovarian cancer,

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mitochondrial dysfunction has been extensively studied using genomics, proteomics, and metabolomics approaches. These studies have identified potential biomarkers and therapeutic targets such as ROS and metabolites, to reverse dysregulated metabolic pathways.

Compared to genomics and transcriptomics, analysis of proteomics is more complex due to the dynamic nature of proteins. While an organism's genome remains relatively constant and mRNA levels provide insights into gene expression, not all mRNAs are translated into proteins. Furthermore, many proteins undergo post-translational modifications, which are critical for their function and add an additional layer of complexity to proteomic analysis. Proteomics has been used extensively in cancer biomarker discovery, offering unique insights into disease mechanisms. Shin et al. summarize LC-MS-based proteomics, highlighting both quantitative proteomics technologies and various sample preparation methodologies critical for robust and reproducible analyses [5]. These studies encompass diverse proteomics technologies, such as data-dependent acquisition (DDA), data-independent acquisition (DIA), and targeted approaches like multiple reaction monitoring (MRM) and parallel reaction monitoring (PRM). Additionally, the authors discuss the integration of proteomics with other Omics data to uncover complex molecular mechanisms and improve biomarker discovery, identifying candidate protein markers from hepatocellular carcinoma (HCC) cell lines and clinical samples including serum, urine, and tissue specimens (both frozen and formalin-fixed and paraffin-embedded). These proteomics analyses enhance the understanding of HCC pathogenesis, while the identified candidate biomarkers show significant potential for advancing diagnosis and prognosis.

The molecular diagnosis of virus-related and cellular biomarkers has proven to be a clinically valuable tool for early cancer detection, treatment monitoring, therapeutic strategy development, and outcome prediction in virus-associated human cancers including nasopharyngeal carcinoma (NPC). NPC is closely associated with Epstein-Barr virus (EBV) infection. EBV, a human herpesvirus, consists of a double-stranded DNA genome of approximately 172 kb. The viral DNA exists as linear DNA within the virion and as circular episome within the host cell nucleus. EBV encodes around 100 viral genes, including both coding and non-coding sequences, which contributes to its pathogenicity and role in NPC development. The molecular markers of EBV in NPC demonstrated a closely linked relationship between viral factors and host cellular signaling pathways. These interactions drive tumor initiation and progression, highlighting the complex crosstalk between EBV and the host cellular environment. Hsu et al. conducted a comprehensive review of various categories of molecular diagnosis for NPC using EBV-related and cellular biomarkers [6]. While numerous candidate biomarkers have been investigated, EBERs (EBER1 and EBER2) detected by in situ hybridization in tissue sections and plasma EBV DNA measured through liquid biopsy biomarkers remain the most widely utilized histological and non-invasive biomarkers for NPC diagnosis and monitoring.

Perspectives

The publications in this special issue highlight the pivotal role of molecular biomarkers in cancer research. Several critical points regarding the clinical utility of biomarkers warrant further investigation:

(1) Clinical trial-based validation. Validation studies conducted in diverse multiple-center populations are essential to establish the clinical relevance of biomarkers.
(2) Non-invasive sample collection. The use of liquid biopsies for non-invasive clinical sample collection is highly encouraged to improve patient compliance and accessibility.
(3) Biomarker panels. Combining a panel of molecular biomarkers, either of the same type or different types, may enhance discriminative power in specific disease scenarios.
(4) Multi-omics, single-cell and spatial approaches. Given the heterogenous nature of cancers, multi-omic integration of biomarker discovery approaches at the single-cell and with spatial resolution hold great potential for advancing personalized medicine.
(5) Cost-effective model systems. Developing cost-effective and time-efficient model systems for preclinical cancer drug screening is crucial for precision treatment and streamlining drug development.

Finally, a collaborative effort involving diverse expertise – clinicians, basic scientists, bioinformaticians, and medical informaticians, biostatisticians, health economists, and biotechnology companies – is vital to accelerate the translation of biomarkers into clinical practice.

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