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Mini-review

Metabolomics in diagnosis and biomarker discovery of colorectal cancer

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ABSTRACT

Colorectal cancer (CRC), a major public health concern, is the second leading cause of cancer death in developed countries. There is a need for better preventive strategies to improve the patient outcome that is substantially influenced by cancer stage at the time of diagnosis. Patients with early stage colorectal have a significant higher 5-year survival rates compared to patients diagnosed at late stage. Although traditional colonoscopy remains the effective means to diagnose CRC, this approach generally suffers from poor patient compliance. Thus, it is important to develop more effective methods for early diagnosis of this disease process, also there is an urgent need for biomarkers to diagnose CRC, assess disease severity, and prognosticate course. Increasing availability of high-throughput methodologies open up new possibilities for screening new potential candidates for identifying biomarkers. Fortunately, metabolomics, the study of all metabolites produced in the body, considered most closely related to a patient's phenotype, can provide clinically useful biomarkers applied in CRC, and may now open new avenues for diagnostics. It has a largely untapped potential in the field of oncology, through the analysis of the cancer metabolome to identify marker metabolites defined here as surrogate indicators of physiological or pathophysiological states. In this review we take a closer look at the metabolomics used within the field of colorectal cancer. Further, we highlight the most interesting metabolomics publications and discuss these in detail; additional studies are mentioned as a reference for the interested reader.

1. Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and cause of cancer-related deaths worldwide [1]. CRC diagnosis and therapy remain dependent upon descriptive classification and staging systems, based primarily on morphology and histology [2,3]. Despite an increased understanding of the molecular pathogenesis of CRC during the past two decades, reliable and robust biomarkers to enable screening, surveillance, and primary prevention of this disease are lacking. Importantly however, there are no markers currently available, to predict CRC in early diagnosis, therefore, the diagnosis and management of CRC continue to be an overwhelming challenge [4]. Metabolomics, a dynamic portrait of the metabolic status of living systems, offers potential advantages through discovery of a suite clinically relevant biomarker which are simultaneously affected by the CRC [5,6]. Because small changes in body can lead to large changes in metabolite levels, the metabolome can be regarded as the amplified output of a biological system. Monitoring fluctuations of certain metabolite levels in body fluids, has become an important way to detect early stages in CRC [7,8].

Metabolomics represents one of the new omics sciences and capitalizes on the unique presence and concentration of small molecules in fluids to construct a 'fingerprint' that can be unique to the individual states [9]. By applying advanced analytical and statistical tools, metabolomics involves the comprehensive profiling of the full complement of low MW compounds in a biological system and can be used to classify CRC on the basis of tumor biology, to identify new prognostic and predictive markers and to discover new targets for future therapeutic interventions. A comprehensive coverage of metabolism can be achieved by a combination of analytical approaches including mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy [10–12].

In the last decade, metabolomics has been applied toward identifying metabolic alterations in CRC that may provide clinically useful biomarkers. Technology and bioinformatics have led to the application of metabolomic profiling to CRC-the high throughput evaluation of a large complement of metabolites and how they are altered by disease perturbations [13]. Recently, high profile publications have drawn attention to the potential of metabolomic analysis to identify biomarkers for early detection or disease progression from readily accessible body fluids [14,15]. This relatively new approach using metabolomics has just begun to enter the mainstream of cancer diagnostics and therapeutics. Here we intend to explore the potential role of metabolomics in CRC and, highlight the key values of marker metabolites.

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2. Metabolomics technologies: the metabolites hunter

Metabolome is a data-rich source of information concerning all the low-molecular-weight metabolites in body, which can indicate early biological changes to the host due to perturbations in metabolic pathways. The emerging field of metabolomics promises immense potential for early diagnosis, therapy monitoring and for understanding the pathogenesis of many diseases [16]. The technological development is the driving force for advances in identifying marker metabolites. Detecting the disease as early as possible is an important task in cancer medicine. Thus, many technologies have been developed for biomarker discovery in cancer to achieve this aim [17]. There are two major high-throughput tools consisting of NMR and MS used in metabolomics study, and they both can provide complementary snapshots of the metabolome of body fluids [18]. A combined analytical approach can improve the potential to detect metabolic profile alterations in a biological specimen. Multiplatform approaches could provide a more comprehensive understanding of metabolic alterations, because no single analytical tool can accommodate the biochemical diversity in entire metabolome [19,20]. An improved combination of MS and NMR approaches may gain more accurate disease detection and insight into mechanisms of CRC [21].

3. Potential role of small molecule metabolites

Metabolomics allows the simultaneous and relative quantification of thousands of different metabolites within a given sample using sensitive and specific methodologies. The repertoire of small-molecular-weight substances in body fluids are known as the metabolites that are an ultimate product of gene, mRNA, and protein activity. The metabolites are biological indicators of normal biological processes, pathological processes or pharmacologic responses to a therapeutic intervention in clinical practice [22,23]. Integrated analysis of these metabolites may provide a powerful platform for discovering novel biomarkers and detecting cancer [24]. Analyzing metabolic differences between unperturbed and perturbed systems in a disease, can lead to insights into the underlying pathology [25]. With advances in methods and technology, biomarker discovery is one of the newly emerging innovations in the diagnosis and treatment of cancer, measuring the response to treatment, identifying perturbed pathways [26]. Recently, a variety of biomarkers have been developed and serve a key role in diagnosis and management, monitoring treatment response of human diseases [27–29]. Validation of biomarkers may entail intensive use of labor and technology and generally requires a large number of study participants as well as laboratory validation studies.

4. Metabolic characteristics of CRC

CRC is the common cause of death from cancer in the world. The limitations of the currently available methods for CRC management highlight the necessity of finding novel markers. Therefore, there is an underlying necessity to discover tumor-specific markers that may serve as molecular targets for the imaging of CRC. Metabonomics can be used to search for potential markers that can provide molecular insight into human CRC, and provides a means for noninvasive screening of tumor-associated perturbations in metabolism. Understanding the metabolome will not only provide insights into the critical sites of regulation, but will also assist in identifying intermediate or surrogate cancer biomarkers for establishing preemptive/preventative or therapeutic approaches [30]. Recently, there has been a growing applications of metabolomics aimed to finding marker metabolites that allows recognition of the critical metabolic pathways in CRC, which could assist diagnosis, provide therapy guidance, and evaluate response to CRC.

5. Bringing metabolomics into the forefront of CRC research: the sooner, the better

CRC is one of the most commonly diagnosed cancers and cause of cancer-related deaths worldwide. The five-year survival rate for CRC caught early is about 50% -but catching it early is incredibly difficult, because symptoms typically appear only during advanced stages of disease. Once the cancer has spread, the survival rate drops to just 1%. Ideally, screening tools and diagnostics would not only be able to detect early signs of cancer, but also differentiate between harmless changes and abnormalities that precede the disease. Traditional tests remain the effective means to diagnose CRC, but this approach suffers from poor patient compliance. Many diseases result in specific and characteristic changes in the chemical and biochemical profiles of biological fluids and tissues prior to development of clinical symptoms [31–33]. Using biomarkers to select the most at-risk population, to detect the disease while measurable and yet not clinically apparent has been the goal of many investigations. Metabolomics promises to be a valuable tool in the early detection of CRC that may enable earlier treatment and improved clinical outcomes. Advantages of metabolomics over other "omics", include its high sensitivity and its ability to enable the analysis of relatively few metabolites compared with the unwieldy number of corresponding genes or mRNA molecules [34,35]. Potential roles for metabolomics in the clinical trials of CRC include biomarker discovery and validation, molecular target discovery, therapy decisions, and patient monitoring [36–39]. Integration of metabolomics into the CRC would be the direction to enable a revolution for future health cares, also perhaps it is time to embrace the arrival of 'CRC–OMICS' era.

6. Metabolomics studies on CRC

Recently, several molecules were found to be specifically expressed in CRC, and these novel molecular markers are reported to improve the sensitivity of cytology or biopsy. Serum samples of patients suffering from colon cancer and controls were collected to analyze metabolic alterations [40]. It revealed multiple significant disease-associated alterations in the amino acid profile with promising diagnostic power. To improve the quality of life of CRC patients, it is important to establish new screening methods for early diagnosis of CRC. Nishiumi et al. had performed serum metabolome analysis using GC/MS established a CRC prediction model [41]. It was composed of 2-hydroxybutyrate, aspartic acid, kynurenine, and cystamine, and its AUC, sensitivity, specificity, and accuracy were 0.9097, 85.0%, 85.0%, and 85.0%, respectively. This prediction model established via GC/MS-based serum metabolomic analysis is valuable for early detection of CRC and has the potential to become a novel screening test for CRC. Sera from CRC patients were analyzed by NMR spectroscopy and GC–MS [42]. In CRC, the serum metabolomic profile changes markedly with metastasis, and site of disease also appears to affect the pattern of circulating metabolites. It may have clinical utility in enhancing staging accuracy and selecting patients for surgical or medical management.

In a study, a GC × GC/TOFMS was developed for the tissue-based global metabonomic profiling of CRC [43]. Results showed that the metabotype associated with CRC is distinct from that of normal tissue and led to the identification of chemically diverse marker metabolites. Metabolic pathway mapping suggested deregulation of various biochemical processes such as glycolysis, Krebs