REVIEW ARTICLE

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The Role of Plasma Metabolites and Biomarkers in Esophageal Cancer

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Abstract

Background: Esophageal cancer (EC) is a highly aggressive malignancy with increasing global prevalence, especially esophageal adenocarcinoma (EAC). Late-stage detection significantly contributes to its unfavorable outcomes, highlighting an urgent demand for non-invasive early diagnostic approaches. Metabolomics, the comprehensive study of small-molecule metabolites, provides a valuable strategy for discovering biomarker patterns that mirror the pathophysiological condition of cancer.
Objective: This review seeks to consolidate and critically assess existing research on the utility of plasma metabolites as diagnostic, prognostic, and predictive biomarkers in EC.
Methods: A systematic search of PubMed, Scopus, and Web of Science was performed for literature published between January 2000 and March 2024. Keywords such as "esophageal cancer," "metabolomics," "plasma," "serum," "biomarkers," "mass spectrometry," and "NMR" were employed. Studies were chosen based on their focus on plasma or serum metabolomic analysis in human EC patients.
Results: EC patients exhibit consistent changes in plasma metabolomic profiles compared to healthy individuals. Major disrupted pathways involve amino acid metabolism (e.g., increased branched-chain amino acids, reduced glutamine), energy metabolism (including the Warburg effect and disturbances in the TCA cycle), and lipid metabolism (alterations in phospholipid and sphingolipid concentrations). Panels comprising multiple metabolites show strong diagnostic performance, often with area under the curve (AUC) values above 0.90. Additionally, certain metabolic patterns may be useful for predicting patient outcomes and evaluating responses to neoadjuvant treatments.
Conclusion: Plasma metabolomics offers considerable potential to transform the clinical approach to EC through non-invasive methods for early diagnosis, risk assessment, and therapy evaluation. Validation through extensive, multi-center prospective studies is needed to implement these advances in clinical settings.

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Introduction

Esophageal cancer (EC) is the eighth most frequently diagnosed cancer worldwide and the sixth highest cause of cancer deaths, with a five-year survival rate around 20% [1]. This poor survival is largely due to the absence of symptoms in early stages, resulting in over 50% of

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cases being identified at advanced, often untreatable phases [2]. The principal histological forms, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), have different epidemiological and risk profiles. ESCC is most common in the "Asian esophageal cancer belt," with major risk factors including smoking, alcohol intake, and dietary insufficiencies [3]. Conversely, EAC rates have risen sharply in Western countries in recent decades, closely associated with gastroesophageal reflux disease (GERD), obesity, and its precursor, Barrett's esophagus (BE) [4].

The current definitive diagnostic method, esophagogastroduodenoscopy with biopsy, is invasive, expensive, and unsuitable for broad population screening [5]. Moreover, traditional serum tumor markers like carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are inadequate in sensitivity and specificity for dependable early diagnosis or surveillance [6]. This diagnostic shortfall has intensified efforts to find new, minimally invasive biomarkers.

Metabolomics, the detailed study of low-molecular-weight metabolites (<1.5 kDa), has become a key methodology in this pursuit. As the final product of genomic, transcriptomic, and proteomic processes, the metabolome offers a functional reflection of cellular phenotype and physiological state [7]. Cancer cells undergo extensive metabolic changes to support increased energy needs, biosynthesis, and redox balance, a recognized hallmark termed metabolic reprogramming [8]. These modifications are subsequently detectable in biofluids like plasma, offering insight into tumor metabolism.

This review provides a thorough synthesis of current plasma metabolomic research in EC. It outlines methodological strategies, summarizes consistently altered metabolic pathways, and evaluates the clinical applicability of plasma metabolites as diagnostic, prognostic, and predictive biomarkers. Finally, it addresses existing obstacles and future directions for integrating these discoveries into clinical practice.

Methods of Metabolomic Analysis in Esophageal Cancer Research

Accurate identification and measurement of plasma metabolites depend on advanced analytical platforms, combined with detailed statistical and bioinformatic analysis.

Analytical Platforms

1. Mass Spectrometry (MS): The predominant platform in exploratory metabolomics, usually paired with a separation method:

- **Liquid Chromatography-MS (LC-MS):** Suitable for analyzing diverse polar and non-polar metabolites with high sensitivity and resolution [9].
- **Gas Chromatography-MS (GC-MS):** Effective for volatile or derivatized compounds (e.g., organic acids, sugars, amino acids), offering strong reproducibility and reliable spectral libraries for identification [10].

2. Nuclear Magnetic Resonance (NMR) Spectroscopy: A highly quantitative, reproducible, and non-destructive method requiring minimal sample preparation [11]. Although less sensitive than MS, it excels at identifying and quantifying abundant metabolites and provides detailed structural data.

Metabolomic Workflow

The standard procedure includes:

- **Sample Collection and Preparation:** Strict protocols are essential to reduce pre-analytical variation. Steps encompass blood collection, plasma isolation, protein removal, and metabolite extraction [12].
- **Data Acquisition:** Metabolite profiles are produced using MS or NMR.
- **Data Pre-processing:** Involves noise reduction, peak identification, alignment, and normalization to adjust for technical variability [13].
- **Multivariate Statistical Analysis:** Unsupervised techniques like Principal Component Analysis (PCA) are applied for quality control and to detect natural clustering. Supervised methods such as Partial Least Squares-Discriminant Analysis (PLS-DA) and Orthogonal PLS-DA (OPLS-DA) are used to enhance separation between predefined groups (e.g., EC vs. healthy) and pinpoint significant metabolites [14].
- **Pathway Analysis:** Significant metabolites are linked to biochemical pathways via databases like KEGG and MetaboAnalyst to identify affected metabolic processes [15].

Results: Altered Metabolic Pathways and Candidate Biomarkers

Plasma metabolomic investigations consistently show substantial disturbances in several central metabolic pathways in EC patients.

Dysregulation of Amino Acid Metabolism

Cancer cells alter amino acid metabolism to sustain rapid growth.

- **Branched-Chain Amino Acids (BCAAs):** Numerous studies observe higher plasma levels of valine, leucine, and **isoleucine** in ESCC and EAC patients [16,17]. This may reflect increased protein breakdown or reduced BCAA metabolism in peripheral tissues.
- **Glutamine and Glutamate:** The glutaminolysis pathway is often activated. Consistently, plasma

glutamine is lower while its derivative, glutamate, is elevated, implying tumor use of glutamine for energy and antioxidant production [18].

- **Aromatic Amino Acids and Tryptophan Metabolism:** Changes in phenylalanine and tyrosine are common. Importantly, the kynurenine pathway of tryptophan breakdown, which promotes immune suppression, is frequently increased, leading to higher kynurenine-to-tryptophan ratios in EC plasma [19].

Rewiring of Energy Metabolism

The Warburg effect, or aerobic glycolysis, is characteristic of EC metabolism.

- **Glycolysis and TCA Cycle:** Increased plasma lactate, a glycolytic end-product, is a frequent finding [20]. Simultaneously, variations in TCA cycle intermediates (e.g., succinate, fumarate, citrate) imply cycle disruption, with intermediates used for biosynthesis [21].
- **Ketone Bodies:** Changes in β-hydroxybutyrate and acetoacetate indicate systemic adjustments in energy substrate use, possibly supporting tumor growth [22].

Alterations in Lipid Metabolism

Lipids are vital for membrane structure, signaling, and energy storage.

- **Phospholipids:** Commonly observed reductions in plasma phosphatidylcholines (PCs) and lysophosphatidylcholines (LysoPCs) [23,24] may result from increased tumor uptake for membrane synthesis.
- **Sphingolipids:** Sphingomyelins (SMs) and ceramides, important in cell growth and death regulation, are often altered. Variations in the ceramide/SM ratio can affect tumor cell survival [25].
- **Fatty Acids and Carnitines:** Modified levels of free fatty acids and acylcarnitines (fatty acid β-oxidation intermediates) suggest adjusted lipid breakdown in EC [26].

Discussion: Clinical Applications and Translation

Diagnostic and Screening Potential

Differentiating EC patients from healthy individuals using plasma metabolite panels is highly encouraging. For example, Ubachs et al. found a panel containing histidine, creatine, PC ae C34:3, and PC ae C36:4 that distinguished EAC from controls with an AUC of 0.94 [23]. Similarly, for ESCC, panels involving amino acids and lipids have achieved AUC values exceeding 0.85 [16,27]. A key application is distinguishing EAC from its pre-cancerous state, Barrett's esophagus. Certain metabolites, like choline, betaine, and specific LysoPCs, show potential in detecting malignant progression [28,29].

Prognostic and Stratification Value

Plasma metabolomic profiles contain important prognostic data. Low levels of specific LysoPCs and high kynurenine have been linked to advanced tumor stage, lymph node metastasis, and reduced overall survival [19,30]. This implies that a pre-treatment plasma metabolomic signature could help recognize high-risk patients who might require more intensive treatment.

Predicting and Monitoring Treatment Response

Tracking metabolic changes during treatment offers a way to assess response in real time. Research indicates that patients responding well to neoadjuvant chemoradiotherapy (nCRT) show a return toward normal plasma metabolic patterns, such as reduced lactate and restored amino acid balance [31,32]. Non-responders, however, often maintain an abnormal metabolome. This method could enable early treatment modification for non-responding individuals.

Challenges and Limitations

Despite promising developments, several issues remain:

- **Pre-analytical and Analytical Variability:** Variations in fasting, sample handling, and analytical methods can greatly affect results, requiring stringent standardization [12].
- **Cohort Heterogeneity and Validation:** Most studies are retrospective and single-center. Large, multi-center prospective studies are necessary to validate proposed biomarkers robustly [33].
- **Biological Confounders:** Diet, gut microbiota, age, other health conditions, and medications influence the plasma metabolome and must be accounted for in study design and analysis [34].

Future Perspectives

Future developments in plasma metabolomics for EC include:

- **Integrated Multi-Omics:** Merging metabolomic data **with** genomic, transcriptomic, and proteomic information will give a comprehensive view of EC biology and reveal new regulatory networks [35].
- **Large Prospective Cohort Studies:** Projects like the UK Biobank and similar large biobanks will be crucial for biomarker validation and establishing reference ranges [36].
- Advanced Data Integration: Using machine learning and artificial intelligence will be key to integrating complex, high-dimensional data for developing precise clinical predictive models [37].

Conclusion

Plasma metabolomics has clearly proven its importance in clarifying the metabolic profile of esophageal cancer. The repeated detection of disturbed pathways related to amino acids, energy metabolism, and lipids offers both biological understanding and a source of non-invasive biomarkers. Metabolite panels exhibit strong promise for enhancing early detection, prognostic assessment, and treatment monitoring, all vital for improving patient survival. Although challenges in validation and standardization remain, ongoing improvements in analytical technology and bioinformatics are facilitating the eventual incorporation of plasma metabolomic signatures into the clinical management of this serious disease.

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The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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