



The Interplay Between Neuroendocrine Hormones, Proteomic Biomarkers, and Altered Biochemical Pathways in Esophageal Adenocarcinoma and Squamous Cell Carcinoma

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Abstract

Esophageal cancer remains a highly aggressive gastrointestinal malignancy with a dismal prognosis worldwide. It is characterized primarily by two distinct histological subtypes: Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EAC). While ESCC is epidemiologically linked to tobacco smoke and alcohol consumption, EAC is closely associated with obesity, gastroesophageal reflux disease (GERD), and Barrett's esophagus (BE). Despite their distinct etiologies, both subtypes undergo severe molecular alterations that involve neuroendocrine shifting, altered systemic proteomic networks, and metabolic reprogramming. Traditional staging relies heavily on invasive tissue biopsies, emphasizing the critical need for non-invasive, blood-based multi-analyte monitoring. This comprehensive academic review systematically evaluates the intricate interplay between neuroendocrine hormones, functional proteomic biomarkers, and altered biochemical pathways in ESCC and EAC to outline novel diagnostic panels and targeted therapeutic strategies.

A methodical review of peer-reviewed articles, clinical trials, and multi-omics validation cohorts published up to late 2026 was performed using specialized databases including PubMed, Web of Science, and Google Scholar. Structural query configurations combined targeted strings: ("esophageal squamous cell carcinoma" OR "esophageal adenocarcinoma") AND ("neuroendocrine hormones" OR "proteomics") AND ("biochemical pathways" OR "leptin" OR "adiponectin" OR "S100A8"). Interventions investigating generalized gastric or intestinal malignancies without sub-classified esophageal longitudinal validation data were excluded.

The biochemical landscapes of ESCC and EAC reveal distinct enzymatic and systemic networks. In EAC, visceral obesity drives a prominent adipokine imbalance. Hypertrophic adipocytes overproduce the pro-inflammatory hormone leptin while suppressing high-molecular-weight (HMW) adiponectin. Elevated leptin binds to its receptor (Ob-R), stimulating Jan kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) and mitogen-activated protein kinase (MAPK) cascades, which accelerate tumor proliferation and suppress pyroptosis. Conversely, adiponectin acts as a critical tumor suppressor, but its systemic depletion promotes tumor migration. In ESCC, serum proteomic profiling reveals a distinct up-regulation of the S100A8/A9 complex,

Alpha-1-Acid Glycoprotein 1 (SAA1), and key glycolytic enzymes such as Enolase 1 (ENO1).

These altered proteomic networks mirror the systemic Warburg effect, where carbohydrate utilization is heavily reduced in favor of accelerated amino acid and sphingolipid catabolism. Furthermore, both subtypes exhibit variable neuroendocrine features; advanced neuroendocrine differentiation correlates with heightened tumor invasion, neoangiogenesis via vascular endothelial growth factor A (VEGF-A), and resistance to standard fluorouracil-based chemotherapies. Esophageal malignancies are driven by a dynamic web of hormonal dysregulation, proteomic shifts, and metabolic adaptations. Transitioning from standalone diagnostic metrics toward multi-analyte panels that combine adipokine ratios (leptin/adiponectin), specific serum proteins (S100A8, ENO1), and angiogenic parameters offers a powerful, non-invasive platform for early detection, prognosis tracking, and personalized target selection.

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Introduction

Esophageal cancer represents one of the most clinically lethal malignancies of the digestive tract, maintaining a position as a leading cause of oncological mortality worldwide. The disease is defined by a striking geographical variation and a distinct binary classification based on histopathological and anatomical characteristics. Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EAC). ESCC originates from the stratified squamous epithelium lining the upper and middle thirds of the esophagus and remains highly prevalent across the "esophageal cancer belt" extending from Central Asia to Northern China, primarily driven by chronic mucosal irritation from heavy tobacco smoke, alcohol intake, and the consumption of scalding hot liquids. Conversely, the incidence of EAC has risen rapidly in Western nations. EAC develops within the distal third of the esophagus, arising from glandular metaplasia (Barrett's esophagus) secondary to chronic gastroesophageal reflux disease (GERD) and visceral obesity.

Despite their distinct environmental triggers and anatomical origins, both ESCC and EAC exhibit highly aggressive behaviors characterized by rapid local invasion, early lymphatic dissemination, and

poor long-term survival rates. For decades, the gold standard for clinical diagnosis and risk stratification has relied on endoscopy coupled with histopathological tissue biopsy. However, anatomical monitoring often fails to detect early malignant transitions; by the time dysphagia or significant weight loss prompts a clinical evaluation, the majority of patients present with locally advanced or metastatic disease [1].

To bridge this diagnostic gap, modern oncology has focused on identifying blood-based liquid biopsy parameters and circulating molecular markers. Cellular transformations within the esophageal microenvironment disturb systemic biochemical pathways long before macroscopic anatomical changes are visible. Malignant cells continuously interact with their surrounding stroma, shedding functional proteins, altered nucleic acids, and signaling molecules into the peripheral circulation [1, 2].

Recent developments in high-throughput mass spectrometry and targeted proteomics have revealed that esophageal carcinogenesis involves an intricate network of biochemical modifications. This review details the molecular landscapes of esophageal cancer by examining the biological impacts of adipokine and neuroendocrine hormone shifts, evaluating diagnostic

serum proteomic panels, and mapping systemic metabolic reprogramming. By linking these distinct pathways, this paper outlines a multi-mechanistic approach designed to improve early screening accuracy and optimize targeted treatment regimens [3].

Methods

To examine the complex network of neuroendocrine shifts, proteomic profiles, and altered metabolic pathways in ESCC and EAC, a structured literature search was performed. Electronic engines, including PubMed, Web of Science, and Google Scholar, were queried for high-impact peer-reviewed research papers, prospective cohort studies, multi-center retrospective validation matrices, and systematic reviews published through late 2026 [3].

The database search structure utilized precise combinations of keywords linked by Boolean operators: ("esophageal squamous cell carcinoma" OR "ESCC" OR "esophageal adenocarcinoma" OR "EAC") AND ("neuroendocrine hormones" OR "leptin" OR "adiponectin") AND ("proteomic biomarkers" OR "S100A8" OR "ENO1") AND ("metabolic pathways" OR "Warburg effect" OR "sphingolipid metabolism"). The article selection criteria prioritized human clinical data involving serum, plasma, or matched tissue specimens [4].

Special attention was given to multi-omics validation studies that combined high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), next-generation sequencing (NGS), and ultra-sensitive multiplex immunoassays [5]. Studies focusing generally on gastrointestinal malignancies without explicit longitudinal data sub-classified for the esophagus were systematically excluded to preserve anatomical and biochemical precision.

Results

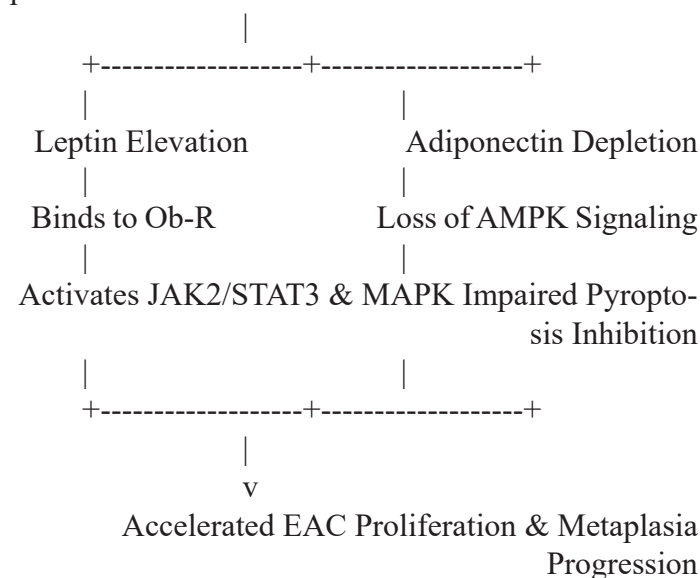
Neuroendocrine Hormone Shifts and Adipokine Imbalances

Adipokine Disruption in Esophageal Adenocarcinoma (EAC)

The development of Esophageal Adenocarcinoma is closely linked to visceral obesity, a condition that functions as an active neuroendocrine disruptor rather than a simple state of excess fat storage [6]. In individuals with abdominal obesity, visceral adipocytes

undergo significant hypertrophy and localized hypoxia, triggering a chronic, low-grade inflammatory state within the adipose tissue. This cellular stress leads to a severe imbalance in circulating adipokines, characterized by the overproduction of the pro-inflammatory hormone leptin and the concurrent suppression of high-molecular-weight (HMW) adiponectin [7, 8].

Visceral Obesity ---> Adipocyte Hypertrophy & Hypoxia



Elevated systemic leptin levels play a direct role in driving progression across the Barrett's esophagus-to-EAC continuum. Leptin binds specifically to its transmembrane receptor (Ob-R) expressed on metaplastic epithelial cells, initiating downstream signaling through the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) and mitogen-activated protein kinase (MAPK) pathways [6]. These signaling networks upregulate cell cycle proteins (such as Cyclin D1) and anti-apoptotic factors (such as Bcl-2), promoting uncontrolled cellular proliferation.

In contrast, HMW adiponectin normally serves as a protective tumor suppressor by activating Adenosine Monophosphate-Activated Protein Kinase (AMPK) signaling, which downregulates the mammalian target of rapamycin (mTOR) pathway and encourages cell death via pyroptosis [9]. Therefore, a rising systemic leptin-to-adiponectin ratio acts as a reliable biochemical indicator of an environment that supports malignant transformation in the distal esophagus [7].

Neuroendocrine Differentiation and Vascular Drivers

Beyond adipokine networks, a subset of esophageal malignancies displays features of neuroendocrine differentiation. True Esophageal Neuroendocrine Carcinoma (ENEC) is a highly aggressive variant, but standard ESCC and EAC adenocarcinomas can also contain scattered neuroendocrine cells that secrete functional peptides, including Chromogranin A (CgA) and Neuron-Specific Enolase (NSE) [10].

Clinical evaluations demonstrate that advanced neuroendocrine differentiation correlates with heightened tumor aggressiveness and increased metastatic potential. These neuroendocrine components release soluble paracrine factors into the local microenvironment, stimulating the secretion of Vascular Endothelial Growth Factor A (VEGF-A) and Transforming Growth Factor-beta 1 (TGF- β 1) from surrounding stromal cells [9].

Elevated pretreatment serum levels of VEGF-A (specifically values exceeding 250 pg/ml) and TGF- β 1 serve as strong indicators of poor treatment response. These factors drive neoangiogenesis, support desmoplasia, and suppress local immune responses, leading to significantly lower pathological complete response (pCR) rates following standard neoadjuvant chemoradiotherapy [10-12].

Serum Proteomic Biomarker Signatures

Advanced serum proteomic profiling using tandem mass spectrometry has identified specific protein signatures that differentiate esophageal cancer patients from healthy controls. These blood-based markers directly reflect the pathological changes occurring within the esophageal tissue microenvironment [5].

The S100A8/A9 and SAA1 Inflammatory Axis

Serum proteomic screens have identified the S100A8/A9 complex (calprotectin) and Serum Amyloid A1 (SAA1) as key indicators of esophageal malignancy [5]. S100A8 and S100A9 are calcium-binding proteins that are highly upregulated and secreted by both tumor cells and infiltrating neutrophils within the tumor microenvironment [13].

Once released into the bloodstream, the S100A8/A9 complex acts as an endogenous ligand for the Receptor for Advanced Glycation Endproducts (RAGE) and Toll-like Receptor 4 (TLR4). This binding initiates a pro-inflammatory signaling cascade that recruits myeloid-derived suppressor cells (MDSCs) to the

tumor site, creating an immunosuppressive environment that assists the tumor in escaping immune surveillance [13]. Simultaneously, elevated SAA1 reflects the body's systemic response to chronic, tumor-mediated tissue inflammation, serving as an effective proteomic marker for tracking disease progression [5].

Glycolytic Proteomic Shift: ENO1 and TPI1

In addition to inflammatory proteins, proteomic assays regularly detect elevated serum levels of core metabolic enzymes, such as Enolase 1 (ENO1), Triosephosphate Isomerase 1 (TPI1), and Phosphoglycerate Mutase 1 (PGAM1) [5]. Under normal physiological conditions, these enzymes are confined within the cellular cytoplasm to facilitate glucose metabolism.

However, because esophageal tumor cells dramatically increase their glycolytic rate, these enzymes are overexpressed and shed into the extracellular fluid through vesicle release or cell lysis [14]. Elevated circulating levels of ENO1 and TPI1 provide a direct, blood-based reflection of the metabolic adaptations supporting rapid tumor growth, making them valuable components for early diagnostic biomarker panels [5].

Altered Biochemical and Metabolic Pathways

The systemic impact of esophageal cancer is further characterized by widespread metabolic reprogramming, which can be measured through plasma and serum metabolomics [2]. Rather than being confined to the local tumor tissue, these metabolic shifts significantly alter the concentrations of circulating metabolites throughout the vascular system [15].

Amino Acid Reprogramming and Glutamatergic Flux

High-resolution liquid chromatography-mass spectrometry (LC-MS) reveals consistent disruptions in amino acid metabolism in patients with esophageal cancer [3]. Systemic levels of L-tryptophan and 5-hydroxyindoleacetic acid are regularly depleted in peripheral blood [15]. This depletion is driven by the tumor's upregulation of indoleamine 2,3-dioxygenase (IDO), an enzyme that degrades tryptophan to produce kynurenine byproducts, which directly inhibit local T-cell proliferation and function [14].

Concurrently, plasma profiles show a substantial drop in free glutamine, coupled with a sharp elevation in glutamic acid [2]. Esophageal tumor cells aggressively

consume extracellular glutamine, utilizing the enzyme glutaminase to convert it into glutamate. This glutamate is then funneled into the tricarboxylic acid (TCA) cycle via alpha-ketoglutarate, providing an essential source of carbon and nitrogen to maintain cell survival and energy production when glucose supplies are limited [16].

Lipid and Sphingolipid Pathway Remodeling

Untargeted lipidomic analyses demonstrate significant alterations in circulating lipid profiles, particularly within the linoleic acid, retinol, and sphingolipid biosynthetic pathways [3]. Multi-omics evaluations combining transcriptomics with tissue mass spectrometry confirm a distinct down-regulation of ceramide synthesis, caused by a decrease in the enzyme degenerative spermatocyte homolog 2 (DEGS2) alongside accelerated catabolism of sphingomyelins into sphingosine-1-phosphate (S1P) [16].

Because ceramide normally functions as an endogenous pro-apoptotic lipid mediator, its rapid clearing and conversion into the pro-survival signaling molecule S1P protects tumor cells from apoptosis [3]. This shift alters systemic lipid and phospholipid ratios, creating a distinct plasma lipid signature that can assist in identifying early-stage ESCC and evaluating patient risk profiles [15].

Discussion

Integrating neuroendocrine, proteomic, and metabolic parameters provides a more cohesive framework for understanding the biology of esophageal cancer, moving clinical management away from relying solely on late-stage structural changes toward early molecular monitoring [1]. As established by international biomarker consensuses, including updates from the Spanish Society of Medical Oncology (SEOM) and Pathology (SEAP), modern clinical care requires the precise evaluation of molecular targets-such as HER2 amplification, programmed death-ligand 1 (PD-L1) expression, and mismatch repair/microsatellite instability (dMMR/MSI) status-to optimize therapeutic selection [17].

However, combining these standard tissue-based markers with circulating biochemical parameters provides a more complete picture of a patient's overall disease state [18].

The distinct biochemical differences between ESCC

and EAC highlight the value of tailored diagnostic approaches. In EAC, the primary drivers are obesity-induced systemic inflammation and adipokine dysregulation [6]. The continuous elevation of the leptin-to-adiponectin ratio provides a clear biochemical baseline for monitoring individuals with Barrett's esophagus, helping to identify those at a higher risk of progression toward adenocarcinoma long before high-grade dysplasia is visible on standard endoscopic mucosal samplings [7]. Furthermore, observing how dietary natural compounds, such as cranberry proanthocyanidins (CPAC), can reverse nearly 42% of reflux-induced protein alterations including pathways regulated by P53, mTORC1, and MYC underscores how targeted metabolic and biochemical interventions can mitigate the inflammatory drivers of EAC [19].

In contrast, managing ESCC benefit significantly from monitoring circulating proteomic panels and amino acid profiles [5]. Serum elevations of the S100A8/A9 complex, ENO1, and glutamate directly mirror the tumor's accelerated glycolytic state and its ability to suppress local immune responses [4]. Utilizing multiplexed next-generation sequencing or high-precision mass spectrometry to track these multi-analyte panels yields diagnostic Area Under the Curve (AUC) scores exceeding 0.90, offering a sensitive, non-invasive option for population-wide screening in high-incidence areas [15].

Additionally, monitoring pre-treatment serum levels of angiogenic and neuroendocrine drivers, such as VEGF-A and TGF- β 1, gives clinicians an effective method for predicting chemotherapy resistance early [2]. This allows for the timely introduction of advanced therapeutic options, such as immune checkpoint inhibitors (e.g., pembrolizumab or nivolumab) or targeted anti-VEGF agents, before structural imaging reveals treatment failure or disease progression [18, 20].

Conclusion and Recommendations

Esophageal adenocarcinoma and squamous cell carcinoma are driven by complex biochemical networks characterized by adipokine imbalances, altered serum proteomic profiles, and systematic metabolic reprogramming. The transition from healthy epithelial regulation to a malignant environment involves the overactivation of leptin-mediated JAK2/STAT3 signaling, the shedding of inflammatory and glycolytic proteins (S100A8/A9, ENO1) into the bloodstream, and

an increased reliance on glutamine and sphingolipid pathway alterations to sustain tumor survival. Utilizing blood-based multi-analyte panels to track these changes offers a non-invasive, scalable strategy to improve early screening accuracy, monitor therapeutic response, and refine personalized treatment selection.

Based on these clinical and molecular insights, the following actions are recommended for oncological research and clinical practice:

- **Development of Subtype-Specific Screening Panels:** Establish and validate blood-based diagnostic panels that combine the leptin/adiponectin ratio for high-risk GERD/Barrett's esophagus surveillance with S100A8/A9 and glycolytic enzyme profiles (ENO1) for early ESCC detection in endemic regions.
- **Pre-Treatment Angiogenic Stratification:** Implement routine serum VEGF-A and TGF- β 1 quantification prior to initiating neoadjuvant chemoradiotherapy to identify patients at risk for treatment resistance, allowing for the earlier integration of targeted anti-angiogenic or immunotherapeutic protocols.
- **Standardization of Pre-Analytical Metabolomic Workflows:** Create uniform guidelines for collecting and processing plasma and serum samples (e.g., using standardized mass spectrometry or ultra-sensitive multiplex immunoassays) to ensure consistent, reproducible biomarker readings across clinical networks.

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