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The Significance of Wnt Signaling Pathway and Its Connection With B-catenin and E-cadherin in Esophageal Adenocarcinoma

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Abstract

Background-Aims: To elucidate the importance of Wnt signaling pathway and its connection with E-cadherin and β-catenin in esophageal adenocarcinoma as well as the expression levels of β-catenin and E-cadherin as potential biomarkers.

Methodology: The study was retrospectively collected by the archives of the First Laboratory of Pathology of the Medical School of the National and Kapodistrian University in Athens, Greece. Seventy-one (n=71) patients with Esophageal Adenocarcinoma (EA) were included in this two years study (2023-2025) to examine the association between β-catenin and esophageal adenocarcinoma.

Results: A total of 71 histopathologically confirmed cases of esophageal adenocarcinoma were analyzed. Immunohistochemical assessment of E-cadherin and β-catenin expression revealed a moderate positive correlation between cytoplasmic β-catenin levels and Tumor Regression Grade (TRG). Furthermore, a strong positive correlation was observed between cytoplasmic and nuclear expression of b-catenin, suggesting that increased cytoplasmic accumulation is associated with enhanced nuclear localization, indicative of Wnt pathway activation. Additionally, a positive correlation was identified between E-cadherin expression and TRG, whereby higher levels of E-cadherin expression were associated with improved therapeutic response.

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Conclusions: Simultaneous targeting of β-catenin and E-cadherin may present a therapeutic strategy in esophageal adenocarcinoma and holds promise for their utilization as prognostic biomarkers.

Keywords: β-catenin, Wnt, E-cadherin, Adenocarcinoma, Esophagus

1. Introduction

1.1 Background

Esophageal cancer ranks as the ninth most commonly diagnosed cancer and the sixth leading cause of cancer-related mortality worldwide (Pickett et al., 2022). Esophageal adenocarcinoma, a major histological subtype, is closely associated with aberrant expression of β-catenin and the trans membrane protein E-cadherin. β-catenin plays a pivotal role in intracellular signal transduction through the Wnt signaling pathway, which is critically involved in the pathogenesis of esophageal cancer (Dourakis et al., 2023). Dysregulation and activation of the Wnt/β-catenin signaling cascade have been documented in a wide range of malignancies, including esophageal cancer.

Moreover, β-catenin remains a vital component of the Wnt signaling pathway, which influences various cellular processes, including gene expression and cellular behavior (Shenoy, 2019). β-catenin and E-cadherin have an important role into cell adhesion and in the development and progression of adenocarcinoma (Lin et al., 2023). Under physiological conditions, β-catenin is bound to E-cadherin at the plasma membrane, contributing to cellular cohesion. The Wnt signaling pathway is directly related to β-catenin and when activated, leads to the accumulation of β-catenin in the cell nucleus, to the transfer of oncogenes and at last to the development of aggressive tumors (Ma et al., 2023).

Surgery, chemoradiotherapy, laser therapy, and electrocoagulation are the most important treatments of esophageal cancer (Huang et al., 2024). The aim of this study is to present the significance of the Wnt signaling pathway and its interplay with E-cadherin and β-catenin in esophageal adenocarcinoma, as well as to investigate the expression levels of β-catenin and E-cadherin as potential prognostic and therapeutic biomarkers.

1.2 Rationale

This research may offer important insights into the molecular mechanisms underlying esophageal adenocarcinoma, potentially highlighting β-catenin and E-cadherin as significant contributors to its development. Additionally, the expression levels of β-catenin and E-cadherin could be used as biomarkers to aid in the diagnosis and treatment of EA, with the potential to enhance patient outcomes.

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1.3 Objectives

(a) to elucidate the significance of Wnt signaling pathway and its connection with β-catenin and E-cadherin in esophageal adenocarcinoma; (b) to examine potential correlations between β-catenin and E-cadherin expression; and (c) evaluate the feasibility of using β-catenin and E-cadherin as biomarkers for early detection or as targets for therapeutic intervention.

1.4 Hypothesis for the study

This study hypothesizes that the dysregulation of β-catenin and E-cadherin may be implicated in the initiation and progression of esophageal adenocarcinoma. In particular, aberrant activation or overexpression of β-catenin, alongside diminished or altered E-cadherin expression, may disrupt cell–cell adhesion and facilitate the activation of the Wnt signaling pathway. Such molecular alterations could contribute to enhanced cellular proliferation, invasion, and tumor development.

1.5 Research questions

This study focuses on investigating the importance of Wnt signaling pathway and its connection with β-catenin and E-cadherin in esophageal adenocarcinoma.

The research aims to address the following questions:

a) To what extent is there a significant association between β-catenin and E-cadherin expression in esophageal adenocarcinoma tissue, and how does this reflect the functional dynamics of the Wnt signaling pathway?
b) How is β-catenin expression correlated with key clinicopathological features of esophageal adenocarcinoma, and what does this reveal about its role in tumor progression?
c) Can the expression patterns of β-catenin and E-cadherin be utilized as reliable biomarkers for the early detection, prognosis, or therapeutic targeting of esophageal adenocarcinoma?

2. Methodology

2.1 Ethical considerations

This study was conducted in accordance with the ethical standards of the Research Ethics Committee of the Medical School of the National and Kapodistrian University of Athens (NKUA), Greece, which approved the research protocol.

2.2 Study design

The data were obtained from anonymized esophagogastric tissue specimens collected from patients who were diagnosed with esophageal adenocarcinoma. These specimens originated from the A΄ Department of Pathology at the Medical School of the NKUA, Greece.

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2.3 Participant characteristics

71 (n=71) anonymous esophagogastric specimens were evaluated from patients diagnosed with esophageal adenocarcinoma, regardless of prior treatment history. Data was collected between 2023 and 2025. The study population comprised adult male and female patients aged 47 and 94 years, with a median age of 67.08 years. There was a marked male predominance, with males representing 83.1% (n=59), while females represented 16.9% (n=12). The clinicopathological traits of patients are summarized in Table 1.

Table 1. Clinicopathological characteristics of patients

Parameters	**Mean**	**Scale**
Age	67.08	47-94
Gender	**Number**	**Percentage %**
Male	59	83.1 %
Female	12	16.9 %
Location		
GJ (gastroesophageal junction)	22	30.9 %
Non GJ	49	69.1 %
Surgical method		
Total gastrectomy	7	9.9 %
Partial gastrectomy	50	70.4 %
Ivory Lewis	10	14.1 %
Without	4	5.6 %
Histological subtype		
Mucinous adenocarcinoma	2	2.9 %
Ulcerative adenocarcinoma	38	53.5 %
No ulceration	31	43.6 %
Differentiation		
High	2	2.9 %
Medium	46	64.7 %
Low	23	32.4 %
Tumor Regression Grade (TRG)	31	

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1	3	9.7 %
2	0	0 %
3	5	16.2 %
4	12	38.7 %
5	11	35.4 %
Stage T		
T_1	7	9.8 %
T_2	15	21.1 %
T_3	43	60.5 %
T_4	6	8.6 %
Lymph Node Infiltration N		
N_0	38	53.5 %
N_1	8	11.3 %
N_2	14	19.7 %
N_3	11	15.5 %

2.4 Statistical analysis

This retrospective study analyzed biomedical data using statistical techniques to assess differences among selected parameters. Formalin-fixed, paraffin-embedded (FFPE) tissue sections were examined, and correlation-based statistical methods were employed to evaluate the expression levels of two immunohistochemical markers: β-catenin and E-cadherin. A p-value of less than 0.05 was considered indicative of statistical significance. All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software, version 28.0 for Windows (Pocevičiūtė et al., 2022).

3. Results

After the immunohistochemical study of the expression of E-cadherin and β-catenin/Wnt, there was found a very strong positive correlation between cytoplasmic and nuclear β-catenin (r=0.956, $p<0.001$): Increased cytoplasmic expression was associated with increased nuclear expression, indicating activation of the Wnt pathway (Table 2).

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Table 2. Correlation between cytoplasmic and nuclear β-catenin

			Cytoplasmic β-catenin %	Nuclear cytoplasmic β-catenin%
Spearman's rho	Cytoplasmic β-catenin %	Correlation coefficient	1.000	0.956**
		Sig. (2-tailed)	.	0.000
		N	71	71
	Nuclear β-catenin%	Correlation coefficient	0.956**	1.000
		Sig. (2-tailed)	0.000	.
		N	71	71
**. Correlation is significant at the 0.01 level (two-tailed).				

It was also shown that there is a moderate negative correlation between the expression of nuclear β-catenin and TRG (r=-0.389, p=0.031). The higher expression of nuclear β-catenin was correlated with worse response to the treatment. This correlation is statistically significant. Furthermore, a positive correlation was found between E-cadherin expression and TRG (r=0.304, p=0.034). The higher E-cadherin expression was correlated with better response to the treatment. This correlation is also statistically significant (Table 3).

Table 3. Correlation between E-cadherin expression and Tumor Regression Grade (TRG)

			E-cadherin%	TRG
Spearman's rho	E-cadherin%	Correlation coefficient	1.000	0.304
		Sig. (2-tailed)	.	0.034*
		N	31	31
	TRG	Correlation coefficient	0.304	1.000
		Sig. (2-tailed)	0.034*	.
		N	31	31
	*. Correlation is significant at the 0,05 level (two-tailed).			

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4. Discussion

Esophageal adenocarcinoma has been associated with the expression patterns of both nuclear and cytoplasmic β-catenin, as well as the transmembrane protein E-cadherin (Dourakis et al., 2023). β-Catenin is a key intracellular mediator within the Wnt signaling pathway and plays a central role in the initiation and progression of esophageal malignancies (Zhang et al., 2020). In the present study involving 71 patients with esophageal adenocarcinoma, a moderate positive correlation was identified between cytoplasmic β-catenin expression and tumor regression grade (TRG), indicating that increased cytoplasmic B-Catenin levels were associated with an enhanced therapeutic response. This relationship was found to be statistically significant (Borcherding et al., 2018).

Moreover, a very strong positive correlation was observed between cytoplasmic and nuclear β-catenin expression, suggesting a coordinated increase in both compartments, likely reflecting activation of the Wnt signaling pathway. Conversely, nuclear β-catenin expression demonstrated a moderate negative correlation with TRG, indicating that elevated nuclear β-Catenin levels were significantly associated with poorer treatment response (Wang et al., 2013).

A positive correlation was also detected between E-cadherin expression and tumor differentiation, whereby well-differentiated tumors exhibited higher E-cadherin levels. However, this correlation was only marginally statistically significant. Similarly, a statistically significant moderate positive correlation between cytoplasmic β-catenin and TRG was reaffirmed (Han et al., 2024), further supporting the association between increased cytoplasmic expression and improved tumor response to therapy. No statistically significant correlation was found between cytoplasmic β-catenin expression and patient age or gender.

Importantly, a strong negative correlation was observed between E-cadherin and nuclear β-catenin expression (Limani et al., 2024). This finding supports the notion that loss of E-cadherin-mediated cell adhesion may facilitate the nuclear translocation of β-catenin and subsequent activation of the Wnt signaling cascade. These results suggest that both β-catenin and E-cadherin could contribute as valuable prognostic biomarkers in esophageal adenocarcinoma.

5. Conclusions

In conclusion, the findings of this study highlight the significance of the Wnt signaling pathway and its association with β-catenin and E-cadherin in the pathophysiology of esophageal adenocarcinoma. High E-cadherin expression was associated with improved treatment response and lower tumor aggressiveness, whereas increased nuclear β-catenin expression, indicative of Wnt pathway activation, correlated with reduced therapeutic efficacy and greater tumor aggressiveness. The assessment of these molecular markers may provide valuable prognostic information and contribute to the development of targeted therapeutic strategies for esophageal adenocarcinoma.

Author Contributions: A.D. was responsible for designing the study, selecting indicators for analysis and collecting the data. A.B., G.S., F.A. contributed to the writing of the manuscript. E.T., A.C. L. and S.S. were responsible for critical revision and final approval.

Data Availability Statement: The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

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