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Research Article

Retrospective Analysis of CD73 in Gastric Cancer Implications for Pathogenesis, Prognosis and Therapeutic Targeting

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ABSTRACT

Gastric cancer (GC) remains a leading cause of cancer - related mortality globally, with limited effective therapeutic strategies for advanced disease. CD73, a cell surface enzyme that catalyzes the conversion of adenosine monophosphate (AMP) to adenosine, has emerged as a critical regulator of the tumor microenvironment and immune evasion in various malignancies, including GC. This retrospective study aimed to systematically evaluate the expression pattern, clinical significance and prognostic value of CD73 in GC using data from the PubMed database. We analyzed 32 eligible studies published between 2015 and 2024, focusing on CD73 expression in GC tissues versus adjacent normal mucosa, associations with clinicopathological parameters and correlation with patient survival outcomes. Our results revealed that CD73 is significantly up - regulated in GC tissues (pooled odds ratio [OR] = 4.23, 95% confidence interval [CI]: 3.18 - 5.62, $P < 0.001$), with high CD73 expression strongly associated with advanced TNM stage (OR = 2.89, 95% CI: 2.15 - 3.88, $P < 0.001$), lymph node metastasis (OR = 3.12, 95% CI: 2.34 - 4.16, $P < 0.001$) and vascular invasion (OR = 2.56, 95% CI: 1.87 - 3.51, $P < 0.001$). Moreover, elevated CD73 expression was linked to poor overall survival (hazard ratio [HR] = 1.92, 95% CI: 1.61 - 2.30, $P < 0.001$) and disease - free survival (HR = 1.78, 95% CI: 1.45 - 2.18, $P < 0.001$). These findings highlight CD73 as a potential prognostic biomarker and promising therapeutic target for GC, supporting further investigation into anti - CD73 strategies in clinical settings.

Keywords: Gastric cancer; Adenosine monophosphate; Clinicopathological parameters

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, with an estimated 1.1 million new cases and 769,000 deaths in 2020[1]. Despite advances in surgical resection, chemotherapy and immunotherapy, the 5 - year survival rate for advanced GC remains below 30%[2]. The limited efficacy of current treatments underscores the need to identify novel molecular targets and biomarkers to improve patient outcomes.

CD73, encoded by the NT5E gene, is a glycosylphosphatidylinositol (GPI) - anchored ectoenzyme that plays a key role in purinergic signaling by converting extracellular AMP to adenosine[3]. Adenosine, in turn, suppresses immune responses by activating adenosine receptors on immune cells, promoting an immunosuppressive tumor microenvironment (TME)[4]. In recent years, CD73 has gained attention as a potential therapeutic target in cancer, with preclinical and clinical studies demonstrating its involvement in tumor progression, metastasis and resistance to immunotherapy[5].

In GC, emerging evidence suggests that CD73 is dysregulated and associated with aggressive disease features, but a comprehensive retrospective analysis of its clinical significance is lacking. This study aims to synthesize data from PubMed - indexed studies to clarify the role of CD73 in GC pathogenesis, clinicopathological correlations and prognosis, providing a foundation for future translational research.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using the terms («gastric cancer» OR «stomach neoplasm») AND («CD73» OR «NT5E») with filters for English - language articles, human studies and publication dates between January 2015 and June 2024. The last search was performed on June 30, 2024.

Study selection criteria

Inclusion criteria were: (1) studies comparing CD73 expression (at the mRNA or protein level) between GC tissues and adjacent normal gastric mucosa; (2) studies analyzing associations between CD73 expression and clinicopathological parameters (e.g., TNM stage, lymph node metastasis, differentiation grade); (3) studies reporting survival outcomes (overall survival [OS], disease - free survival [DFS]) based on CD73 expression; (4) studies providing sufficient data for extraction of odds ratios (ORs) or hazard ratios (HRs) with 95% CIs. Exclusion criteria included reviews, case reports, in vitro studies without patient data and studies with overlapping cohorts.

Data extraction and quality assessment

Two independent reviewers extracted data, including first author, publication year, country, sample size, CD73 detection method (immunohistochemistry [IHC], qRT - PCR or Western blotting), expression cutoff value and associations with clinicopathological features and survival. Discrepancies were resolved by consensus. Study quality was assessed using the Newcastle - Ottawa Scale (NOS) for observational studies, with scores ≥ 6 indicating high quality.

Statistical analysis

Meta - analyses were performed using Stata 17.0 software. Pooled ORs with 95% CIs were calculated for associations between CD73 expression and clinicopathological parameters. Pooled HRs with 95% CIs were used to evaluate survival outcomes. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test; a random - effects model was applied if $I^2 > 50\%$ or $P < 0.10$, otherwise a fixed - effects model was used. Publication bias was evaluated via Egger's test and funnel plots. $P < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

CD73 expression in GC tissues: CD73 was up - regulated in GC tissues compared to adjacent normal mucosa in 29/32 studies. Meta - analysis showed a significant association between GC and high CD73 expression (pooled OR = 4.23, 95% CI: 3.18 - 5.62, $P < 0.001$), with low heterogeneity ($I^2 = 28.7\%$, $P = 0.08$).

Associations with clinicopathological parameters: High CD73 expression was significantly associated with advanced TNM stage (OR = 2.89, 95% CI: 2.15 - 3.88, $P < 0.001$), lymph node metastasis (OR = 3.12, 95% CI: 2.34 - 4.16, $P < 0.001$), vascular invasion (OR = 2.56, 95% CI: 1.87 - 3.51, $P < 0.001$) and poor differentiation (OR = 1.87, 95% CI: 1.42 - 2.47, $P < 0.001$). No significant association was found with age or gender ($P > 0.05$).

Prognostic significance: Elevated CD73 expression predicted shorter OS (HR = 1.92, 95% CI: 1.61 - 2.30, $P < 0.001$) and DFS (HR = 1.78, 95% CI: 1.45 - 2.18, $P < 0.001$) in GC patients (Figure 3). Subgroup analyses showed consistent results across different geographic regions and detection methods.

Discussion

This retrospective analysis demonstrates that CD73 is significantly up - regulated in GC and associated with aggressive clinicopathological features and poor prognosis. These findings align with preclinical studies showing that CD73 - derived adenosine promotes immune evasion by inhibiting T cell activation and natural killer cell function[6] and enhances angiogenesis by stimulating endothelial cell proliferation[7].

The strong correlation between CD73 overexpression and lymph node metastasis suggests a role in GC dissemination. Mechanistically, CD73 may facilitate epithelial - mesenchymal transition (EMT) via activation of the PI3K/Akt pathway, as observed in vitro[8]. Additionally, CD73 expression is linked to chemotherapy resistance, with high CD73 levels associated with reduced response to 5 - fluorouracil - based regimens[9], possibly due to adenosine - mediated suppression of apoptosis.

Clinically, our data support CD73 as a prognostic biomarker. The consistent association between high CD73 and poor survival across diverse cohorts underscores its potential utility in risk stratification. Furthermore, CD73 inhibition has shown promise in preclinical GC models, with anti - CD73 antibodies enhancing the efficacy of PD - 1/PD - L1 blockade[10]. Ongoing clinical trials are evaluating anti - CD73 therapies in solid tumors, including GC and our findings provide rationale for their inclusion.

Limitations include heterogeneity in CD73 detection methods and cutoff values and the retrospective nature of included studies. Future prospective studies with standardized CD73 assessment are needed to validate these findings.

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