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Research Article

Retrospective Analysis of Colony-Stimulating Factor 1 (CSF-1) in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) remains a leading cause of cancer-related mortality globally, with the tumor microenvironment (TME) playing a critical role in disease progression and treatment resistance. Colony-stimulating factor 1 (CSF-1), a key regulator of macrophage polarization and function, has emerged as a potential biomarker and therapeutic target in GC. This retrospective study aimed to systematically evaluate the expression pattern, clinical associations and prognostic significance of CSF-1 in GC using data from the PubMed database. We analyzed 27 eligible studies published between 2015 and 2024, involving 4,938 patients. Our results showed that CSF-1 expression was significantly upregulated in GC tissues compared to adjacent normal mucosa (pooled standardized mean difference [SMD] = 1.65, 95% confidence interval [CI]: 1.31-1.99, P < 0.001). High CSF-1 expression was associated with advanced TNM stage (odds ratio [OR] = 2.87, 95% CI: 2.21-3.73, P < 0.001), lymph node metastasis (OR = 3.12, 95% CI: 2.40-4.06, P < 0.001), vascular invasion (OR = 2.64, 95% CI: 1.98-3.52, P < 0.001) and poor differentiation (OR = 2.38, 95% CI: 1.82-3.11, P < 0.001). Moreover, elevated CSF-1 levels predicted shorter overall survival (hazard ratio [HR] = 1.83, 95% CI: 1.55-2.16, P < 0.001) and disease-free survival (HR = 1.72, 95% CI: 1.43-2.07, P < 0.001). These findings confirm that CSF-1 is a valuable prognostic biomarker and support its role in regulating immunosuppressive TME in GC.

Keywords: Tumor microenvironment; Gastric cancer; GC tissues

Introduction

Gastric cancer (GC) is characterized by complex interactions between tumor cells and the TME, where immune cells such as tumor-associated macrophages (TAMs) promote angiogenesis, invasion and immune evasion[1]. Colony-stimulating factor 1 (CSF-1), also known as macrophage colony-stimulating factor (M-CSF), binds to its receptor CSF-1R on monocytes/macrophages to induce their recruitment, survival and differentiation into TAMs[2]. TAMs, predominantly of the M2 phenotype, secrete pro-tumorigenic cytokines (e.g., IL-10, TGF-β) and matrix metalloproteinases (MMPs), facilitating tumor progression[3].

In GC, CSF-1 overexpression has been linked to aggressive disease, but inconsistencies exist regarding its prognostic value[4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify CSF-1's expression pattern, clinicopathological correlations and prognostic significance in GC, aiming to inform its potential as a therapeutic target.

Materials and Methods

Data source and search strategy

We systematically searched the PubMed database using the terms («gastric cancer» OR «stomach neoplasm») AND («CSF-1» OR «colony-stimulating factor 1» OR «M-CSF») with filters for English-language articles, human studies and publication dates between January 2015 and December 2024. The last search was performed on January 5, 2025.

Study selection criteria

Inclusion criteria were: (1) studies measuring CSF-1 expression in GC tissues and adjacent normal mucosa; (2) studies analyzing associations between CSF-1 expression and clinicopathological parameters (TNM stage, lymph node metastasis, differentiation, vascular invasion); (3) studies reporting survival outcomes (overall survival [OS], disease-free survival [DFS]) based on CSF-1 levels; (4) studies providing sufficient data to calculate ORs, HRs or SMDs with 95% CIs. Exclusion criteria included reviews, case reports, preclinical studies without patient data and overlapping cohorts.

Data extraction and quality assessment

Two independent reviewers extracted data, including first author, publication year, country, sample size, CSF-1 detection method (immunohistochemistry [IHC], enzyme-linked immunosorbent assay [ELISA], qRT-PCR), cutoff value for high/low expression and associations with clinicopathology/survival. Discrepancies were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS), with scores ≥ 6 indicating high quality.

Statistical analysis

Meta-analyses were performed using Stata 17.0 software. Pooled SMD with 95% CIs was calculated for CSF-1 expression comparisons. Pooled ORs (clinicopathology) and HRs (survival) with 95% CIs were computed. Heterogeneity was assessed via I^2 statistic and 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

CSF-1 expression in GC tissues

CSF-1 expression was significantly higher in GC tissues compared to adjacent normal mucosa (SMD = 1.65, 95% CI: 1.31-1.99, $P < 0.001$), with moderate heterogeneity ($I^2 = 46.8\%$, $P = 0.03$).

Associations with clinicopathological parameters

High CSF-1 expression was strongly associated with advanced TNM stage (OR = 2.87, 95% CI: 2.21-3.73, $P < 0.001$), lymph node metastasis (OR = 3.12, 95% CI: 2.40-4.06, $P < 0.001$), vascular invasion (OR = 2.64, 95% CI: 1.98-3.52, $P < 0.001$) and poor differentiation (OR = 2.38, 95% CI: 1.82-3.11, $P < 0.001$). No significant associations were found with age or gender ($P > 0.05$).

Prognostic significance

Elevated CSF-1 expression predicted shorter OS (HR = 1.83, 95% CI: 1.55-2.16, $P < 0.001$) and DFS (HR = 1.72, 95% CI: 1.43-2.07, $P < 0.001$) (Figure 3). Subgroup analyses showed consistent results across detection methods (IHC: HR = 1.79, 95% CI: 1.48-2.16; ELISA: HR = 1.92, 95% CI: 1.45-2.54).

Discussion

This retrospective analysis demonstrates that CSF-1 is upregulated in GC and associated with aggressive clinicopathological features and poor prognosis, highlighting its role in TAM-mediated tumor progression. CSF-1 recruits circulating monocytes to the TME and polarizes them into M2 macrophages, which promote angiogenesis by secreting VEGF and MMPs[6]. This explains the strong association between high CSF-1 and vascular invasion observed in our study.

Moreover, M2 macrophages suppress anti-tumor immunity by inhibiting T cell proliferation and promoting regulatory T cell (Treg) differentiation[7], which may contribute to the link between CSF-1 and lymph node metastasis. The association between CSF-1 and poor differentiation suggests a role in maintaining a stem-like phenotype in GC cells, as CSF-1 has been shown to activate the PI3K/Akt pathway, enhancing self-renewal and treatment resistance[8].

Clinically, our findings support CSF-1 as a prognostic biomarker. Targeting CSF-1/CSF-1R signalling with inhibitors (e.g., emactuzumab) has shown promise in preclinical GC models, reducing TAM infiltration and restoring anti-tumor immunity[9]. Combining CSF-1R inhibitors with immune checkpoint inhibitors (e.g., anti-PD-1) may enhance therapeutic efficacy by reversing immunosuppression[10].

Limitations include heterogeneity in CSF-1 detection methods and cutoff values. Standardized protocols for CSF-1 assessment are needed for clinical translation. Further studies should explore CSF-1's interaction with other TME factors to identify combinatorial therapeutic strategies.

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