Clinical features and molecular landscape of cuproptosis signature-related molecular subtype in gastric cancer

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Chong, Wei, Huicheng Ren, Hao Chen, Kang Xu, Xingyu Zhu, Yuan Liu, Yaodong Sang, et al. 2024.“Clinical Features and Molecular Landscape of Cuproptosis Signature Related Molecular Subtype in Gastric Cancer.” iMeta 3: e190.https://doi.org/10.1002/imt2.190
Graphical Abstract

Comprehensive characteristics of cuproptosis-related genes in gastric cancer

Clinical Features and Molecular Landscape of Cuproptosis Signature Related Molecular Subtype in Gastric Cancer

Correlation and effectiveness between CSRS score and antineoplastic drugs

The cuproptosis signature clusters characterized by distinct molecular landscapes

Identification of cuproptosis signature clusters and its clinical features

Tumor genomic landscapes in CSRS subtypes

Construction of the cuproptosis signature risk score and exploration of its clinical relevance

Verifying the differences through Western blot experiments and drug sensitivity experiments
The landscape of the mutation of cuproptosis-related genes in gastric cancer

- **16 cuproptosis-related genes**: CDKN2A, ATP7A, ATP7B, DLD, MTF1, LIPT1, DLST, DLAT, GLS, LIAS, PDHB, DBT, FDX1, SLC31A1, GCSH, PDHA1

- **Metascape**: glyoxylate metabolism, glycine degradation, copper metabolism

- Genetic alterations and CNV alterations
RESULTS

Cuproptosis signature patterns characterized by specific clinical features and molecular subtypes

• Four cuproptosis signature clusters (CSC)

• Microsatellite instability (MSI)-positive tumors converged within the CSC1 subtype, culminating in the amalgamation of a hypermutated phenotype, MSI, and an immune-enriched subtype

• CSC4 subtype exhibited a strong correlation with advanced tumor staging, the mesenchymal phenotype, the diffuse histological subtype, and a fibrotic tumor microenvironment (TME) subtype
RESULTS

Cuproptosis signature clusters characterized by distinct molecular processes and genomic alterations

- **Functional signal enrichment:** CSC1 exhibited significant enrichment in processes related to substance synthesis, metabolism, and energy metabolism; CSC4 predominantly showed enrichment in pathways associated with cell adhesion and stromal pathways

- **Mutational landscape:** CSC1 exhibited the highest mutational load and CSC3 had a higher aneuploidy score

- **Immune landscape:** activated CD4+/CD8+ T cells were mainly enriched in the CSC1 subtypes. However, effector memory CD4+/CD8+ T cells, mast cells, eosinophils, Type 1 helper cells, and Type 2 T helper cells were markedly elevated in the CSC4 subtype
Construction of cuproptosis signature risk score and exploration of its clinical relevance

- Specifically, the cuproptosis signature risk score was markedly negatively correlated with lipoic acid, pyruvate metabolism, and the citric acid cycle. Conversely, it showed a positive correlation with signatures related to cancer fibroblasts, tumor-associated macrophages, glycogen and glycosaminoglycan biosynthesis, as well as cytokine receptors.

- DBT, MTF1, and ATP7A were significantly elevated in the CSRS-High subtype; ATP7B, SLC31A1, GCSH, LIAS, DLAT, FDX1, DLD, and PDHA1 were obviously increased in the CSRS-Low subtype in the 3 databases.

- CSRS-High patients exhibit significantly worse prognosis.
Tumor genomic landscapes in Cuproptosis signature mutation gastric cancer

- **ARID1A, PIK3CA, APC, ERBB3, COL11A1, RNF43, BCOR, PTEN, and PTPN23** had higher mutation rates in the CSRS-Low subtype.

- CSRS-Low in patients were significantly associated with higher tumor mutational load.

- and cytobands in **1p36.11 (ARID1A)** and **11q23.2 (FDX1, DLAT, BACE1)** in cuproptosis signature risk high score subtype contained the frequently deleted regions.
Analysis of correlation and effectiveness between CSRS score and antineoplastic drugs

- We further jointly analyzed the Cancer Cell Line Encyclopedia (CCLE) and Genomics of Drug Sensitivity in Cancer (GDSC1) databases to determine the association between CSRS score and antineoplastic drug sensitivity of gastric cancer cell lines.

- Screening out potential small molecule drugs for the treatment of CSRC High gastric cancer patients, such as SB505124, Talazoparib, Thapsigargin, and NSC319726.
RESULTS

Verifying the differences between CSRS-Low (AGS) and CSRS-High (HGC-27) subtypes through Western blot experiments and drug sensitivity experiments

- Western blot analysis revealed: In the CSRS-High subtype of gastric cancer cells, the expression of proteins related to cuproptosis progression was significantly increased, while the CSRS-Low subtype was opposite.

- Drug sensitivity experiments: NSC319726, talazoparib, and thapsigargin have relatively high IC50s in the CSRS-Low subtype of gastric cancer cells
Summary

- Four distinct cuproptosis signature-based clusters are associated with different clinical outcomes and biological pathways and are highly consistent with distinct tumor immune contextures, respectively.
- Based on the cuproptosis signature risk score, GC patients with a higher CSRS score were characterized by decreased survival time and correlated with tumor adhesion state and lower tumor mutation loads.
- *DBT, MTF1,* or *ATP7A* were significantly elevated in the CSRS-High subtype, while *ATP7B, SLC31A1, GCSH, LIAS, DLAT, FDX1, DLD,* and *PDHA1* were increased in the CSRS-Low subtype.
- Drug sensitivity analyses revealed potential therapeutic compounds for GC with high CSRS scores.

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