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# Letter to the Editor: *GEN1* as a potential therapeutic target in gastric cancer

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## Abstract

I thoroughly reviewed the paper by Zhang *et al* published in the recent issue of *World Journal of Gastrointestinal Oncology*, and commend the authors for their in-depth analysis of the oncogenic functions of *GEN1* in gastric cancer (GC). The recent work by Zhang *et al* sheds light on the oncogenic role of *GEN1* in GC, which is involved in cell cycle progression, mitochondrial function, ferroptosis, and chemotherapeutic sensitivity. The findings of this study are of scientific interest and future studies to increase the translational relevance of the work are proposed.

**Key Words:** *GEN1*; Gastric cancer; Ferroptosis; Mitochondrial dysfunction; Cell cycle; Chemotherapy sensitivity

**Core Tip:** Gastric cancer (GC) growth is driven by complex molecular pathways including genomic instability, cell cycle dysregulation, mitochondrial dysfunction, and ferroptosis. Novel data suggest that *GEN1*, a Holliday junction resolvase involved in DNA repair, is a key oncogenic regulator in GC that promotes tumor cell proliferation, migration, survival, and chemoresistance, and modulates ferroptosis-related pathways, suggesting that *GEN1* may be a therapeutic target and that adding molecular markers related to DNA damage responses may enhance diagnostic accuracy and therapy stratification in GC.

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## TO THE EDITOR

Gastric cancer (GC) remains a major public health problem and one of the leading causes of cancer-related death worldwide, despite the progress in surgical methods, chemotherapy, and targeted treatments, the clinical outcomes of advanced gastric cancer remain unsatisfactory and are mainly due to late diagnosis, high genomic heterogeneity, and rapid emergence of therapeutic resistance[1]. There is a clear need to identify new genetic markers that drive tumor progression and therapeutic stratification and response.

GC is highly characterized by pronounced genomic instability, which has a major impact on the aggressiveness of the disease, intratumoral heterogeneity, and resistance to DNA-damaging treatments. Cancer cells adapt to this instability by increasing DNA damage response and repair mechanisms, so they maintain their proliferative capacity in the presence of replication stress. Although many aspects of homologous recombination and DNA repair in GC have been well studied, structure-specific endonucleases involved in resolution of late-stage recombination intermediates have received less attention[2].

*GEN1* is a Holliday junction resolvase that is conserved in eukaryotes and is required to resolve recombination intermediates and prevent aberrant chromosomal structures. Although traditionally considered a genome stability maintenance factor, evidence suggests *GEN1* may be appropriated by cancer cells to enable unregulated growth and survival under genotoxic stress; the functional role of *GEN1* in GC biology and its potential involvement in therapeutic resistance and regulated cell death pathways is not well defined[3-5].

In the case of GC, a relatively recent discovery in cancer research shows that ferroptosis is a key vulnerability, and that iron metabolism, mitochondrial dysfunction, and oxidative stress are related to the fate of tumor cells. Understanding how genome maintenance factors affect metabolic and redox balance may offer new treatment strategies, particularly for cancers with high replication stress[6].

The recent work by Zhang *et al*[1] published in *World Journal of Gastrointestinal Oncology* provides relevant and mechanistically significant evidence that *GEN1* has roles beyond classical DNA repair that affect cell proliferation, migration, apoptosis, ferroptosis, and chemotherapy sensitivity in GC, and using bioinformatic analyses and functional and metabolic experiments, they have demonstrated that *GEN1* is an important regulator linking genomic stability with mitochondrial integrity and apoptotic pathways. Here, we discuss the broader implications and innovative aspects of their findings, as well as important areas for future research that will enhance the translational potential of *GEN1* as a therapeutic target in GC.

GC is one of the most prevalent and aggressive cancers in the world, and the molecular pathways that control cell proliferation, migration, apoptosis, and, more recently, ferroptosis are complex and require further study to discover novel therapeutic options[3-6]. A gene involved in DNA repair and genomic stability, *GEN1*, has been identified as a possible modulator of tumorigenic processes; however, its specific roles in GC still need to be clarified.

The authors used The Cancer Genome Atlas (TCGA)-STAD database, which demonstrated that *GEN1* is substantially upregulated in gastric cancer cell lines. This work employed CellMiner database to corroborate the TCGA results and to determine whether these results are similar in other cancer types (NCI-60)[7] (CellMiner; https://discover.nci.nih.gov/cellminer/home.do). *GEN1* expression was found to be increased in all cancer cell lines used in this database, with only a few exceptions. EnrichR (a comprehensive gene set enrichment analysis web server)[8-10] was employed to understand *GEN1* involvement in biochemical processes to confirm experimental data provided by Zhang *et al*[1].

*GEN1* knockdown resulted in reduced cell migrationand proliferation, while significantly altering apoptotic responses in AGS cells. *GEN1*-associated genes enriched in pathways important for genomic integrity such as the cell cycle, homologous recombination, and the Fanconi anemia pathway were identified through their co-expression analysis. The most significant aspect of this work is the comprehensive study of ferroptosis. *GEN1* knockdown decreased ATP, increased reactive oxygen species, downregulated *FTH1* and *GPX4*, and increased ACSL4, all contributing to mitochondrial dysfunction and increased ferroptotic sensitivity[11]. Ferrostatin-1 rescue tests confirmed that cell death was ferroptosis-dependent, and *GEN1*-deficient AGS cells exhibited significantly increased cisplatin sensitivity, demonstrating that *GEN1* is a modulator of the chemotherapeutic response. The findings of this study are encouraging.

Yet other mechanisms linked to the *GEN1* pathway are still unknown: (1) Non-coding RNA molecules that regulate proliferation in GC[12]; (2) The regulation of ferroptosis has recently received attention in GC, with circular RNAs (circRNAs) implicated in its modulation[13]; and (3) The role of cancer stem cells in GC progression has also been invest-

igated, but gastric cancer stem cells have increased proliferation, migration, invasion, drug resistance, and tumorigenic abilities compared to parental cells. It remains to be explored how stem cells affect *GEN1* pathway. The clinical relevance of this work can be increased by *in vivo* validation, clinicopathological correlations, and molecular subtype analyses.

## Discussion

Combining tumor markers and imaging modalities is critical for modern cancer diagnostics; however, as indicated by recent molecular oncology studies, diagnostic interpretation should be more biologically based on the biology of DNA damage response. Gastrointestinal cancers exhibit dysregulated genome maintenance pathways, which impact tumor behavior, biomarker expression, and imaging features, and hence diagnostic systems need to be more biologically integrated. Here, the role of a structure-specific Holliday junction resolvase, *GEN1*, which is an important regulator of genome stability in GC was elaborated.

*GEN1* is frequently overexpressed in GC and is required for the survival of cancer cells by resolving DNA intermediates associated with replication stress, *GEN1* expression is associated with aggressive clinicopathological features and a poor prognosis, making it a mechanistically relevant biomarker and a potential therapeutic target[11]. These discoveries are critically important because they connect diagnoses and therapeutics, and because molecular markers, such as *GEN1*, may complement traditional tumor markers and imaging by reflecting underlying tumor biology rather than just tumor burden, suggesting that incorporating genetic factors associated with DNA repair, such as *GEN1*, into diagnostic and prognostic models may improve the therapeutic value of tumor markers and imaging techniques, particularly for GC, for which early detection and treatment classification are challenging[11].

Briefly, the study by Zhang *et al*[1] sheds light on the molecular mechanism of *GEN1* biochemistry in GC and provides evidence that *GEN1* can be a therapeutic target, which is an important refinement to the understanding of GC biology. Network pharmacology research also reveals biochemical mechanisms[14] that can provide novel information about tumor biology.

The mechanisms of DNA damage response and ferroptosis have been well studied in GC, but as mechanisms of action, these are largely considered to be mechanistically distinct. Most studies have focused on classical DNA repair factors as "passive guardians" of genomic stability or, on the other hand, ferroptosis as a metabolic vulnerability regulated by iron homeostasis and lipid peroxidation.

This comment and the work that it evaluates are particularly notable for explicitly combining these two research areas using the functional perspective of *GEN1*. It reinterprets *GEN1*, which was previously known mostly as a housekeeping Holliday junction resolvase, as an oncogenic dependency that enables GC cells to tolerate replication stress and at the same time prevent ferroptotic cell death, which places *GEN1* at a previously unexplored intersection between genome maintenance and metabolic-redox regulation. The study goes beyond descriptive expression analysis by linking *GEN1* activity to mitochondrial dysfunction, oxidative stress accumulation, and altered ferroptosis sensitivity factors that are now recognized as major contributors to treatment resistance in GC.

A notable feature is the finding that *GEN1* modulates chemotherapy sensitivity, specifically to cisplatin, and the role of *GEN1* in resistance to platinum-based drugs has been extensively studied; however, most of the previous work has been on drug transport, detoxification mechanisms, or the ability to evade apoptosis. This study extends the mechanistic concept of chemotherapy resistance and suggests that targeting DNA repair enzymes might indirectly restore ferroptotic sensitivity.

Furthermore, this study also contributes to the field by proposing that *GEN1* could serve as a biomarker of tumor intrinsic biology, as opposed to just tumor burden, which is monitored by traditional biomarkers, and that *GEN1* expression may indicate a tumor's ability to survive genotoxic and oxidative stress, which places *GEN1* in a modern precision oncology paradigm where biomarkers inform therapy stratification and combination methods, as opposed to just diagnostic purposes.

The unique aspect of this work is the integration of genomic instability, mitochondrial metabolism, ferroptosis, and chemotherapeutic response into a biological model of *GEN1* that goes beyond incremental characterization to a conceptual advance that may inform future translational studies, such as the development of combination medicines targeting DNA repair and ferroptosis pathways in gastric cancer.

## Future perspectives

There are many promising directions for future research, with the nascent function of *GEN1* in gastric cancer. *In vivo* validation using xenograft and genetically modified mouse models will be necessary to determine whether inhibition of *GEN1* can inhibit tumor growth and increase ferroptosis sensitivity in a physiological setting and evaluate any toxicities associated with targeting a DNA repair enzyme in normal proliferative tissues. The clinical implications of *GEN1* as a biomarker also need to be carefully evaluated; investigating the association between *GEN1* expression and clinicopathological characteristics, molecular subtypes, therapeutic efficacy, and patient survival in large GC cohorts will determine its prognostic and predictive value.

Combining *GEN1* status with existing molecular classifications might improve patient stratification for personalized therapy. Third, mechanistic studies should explore the regulation of *GEN1* at multiple levels, including non-coding RNAs, epigenetic changes, and post-translational control, as well as its potential connections to cancer stem cell-related pathways. The emerging understanding of circRNAs and metabolic regulators in ferroptosis implies that the convergence of these two factors on *GEN1* signaling might open up a new regulatory pathway.

The therapeutic implications of inhibiting *GEN1* are particularly worthy of attention, and the association between GEN1 activity, ferroptosis inhibition, and cisplatin resistance suggest that combinatorial approaches targeting *GEN1* in combination with DNA-damaging drugs or ferroptosis inducers could represent a rational and novel therapeutic strategy. Translation of these principles to preclinical and clinical applications may be accelerated by progress in small-

molecule inhibitors and network pharmacology.

### Limitations

The hypothesis that *GEN1* may serve as a potential therapeutic target in GC is speculative, and its clinicopathological correlations with the existing classification systems are largely absent; to date, there is not convincing evidence that expression or genomic alteration of GEN1 is significantly correlated with TNM (Tumor, node and metastasis) stage and that it plays a critical role in tumor progression, invasion depth, lymph node involvement, and metastatic potential; thus, the therapeutic significance of targeting *GEN1* in GC remains unclear.

Likewise, *GEN1* has not been definitively associated with specific Lauren subtypes, and the lack of a preferred association with either the intestinal or diffuse subtype implies that *GEN1* does not fit within any histogenetic pathway, differentiation state, or stromal interaction that would normally influence subtype-directed therapy, which, in gastric cancer, is usually based on distinct molecular alterations that are highly enriched for and clinically relevant in specific Lauren groups. From a molecular classification perspective, there is no significant correlation between *GEN1* status and Epstein-Barr virus (EBV)-positive or microsatellite instability-high (MSI-H) gastric cancers.

EBV-associated malignancies show recurrent epigenetic alterations and immune-related features, whereas MSI-H tumors show severe defects in mismatch repair and increased mutational burden. *GEN1* enrichment was not observed in either subgroup, which does not support its potential role in the basic biology of these therapeutically relevant entities, and the additional therapeutic benefit of inhibition of *GEN1*-mediated structure-specific endonuclease activity is also not evident in MSI-H gastric cancer, which is characterized by high DNA repair deficiencies.

The contradictory associations among *GEN1*, TNM staging, Lauren classification, and EBV/microsatellite instability molecular subtypes illustrate the difference between mechanistic plausibility and clinical validation in gastric cancer; until *GEN1* is validated to identify a biologically distinct patient subset, predict clinical outcomes, or suggest therapeutic susceptibility in a stratified manner, its designation as a therapeutic target should be considered hypothesis-generating rather than evidence-based in GC.

*GEN1* is known to play a role in DNA repair and Holliday junction closure, but it poses significant druggability challenges due to its lack of well-defined, deep binding pockets that are typically favored for small-molecule control, the protein functioning primarily *via* protein–DNA interactions on a flat and extended nuclease surface, the activity of *GEN1* being stringently regulated in a cell-cycle-dependent manner and mostly redundant with other structure-selective endonucleases, the lack of known endogenous ligands, and the lack of clear structural evidence of allosteric sites, which limits classical drug development methods against *GEN1*, so other strategies, such as indirect pathway modulation, synthetic lethality approaches, or protein–protein interaction inhibitors, may be needed to exploit the DNA repair needs associated with *GEN1*.

### Conclusion

This finding not only adds to the understanding of the biology of gastric cancer but also reassigns *GEN1* from a classical DNA repair factor to a key player at the intersection of genomic stability, mitochondrial function, ferroptosis regulation, and chemotherapy resistance, thus providing a unified and mechanistically coherent model of tumor cell survival under stress. These results emphasize *GEN1* as a potential therapeutic target and a candidate biomarker of intrinsic tumor resistance rather than just tumor burden and further establish a foundation for future translational studies on how the interplay between DNA repair and ferroptosis can be harnessed to improve therapy.

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