Journal Full Title: Journal of Biomedical Research & Environmental Sciences


Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 133

Issue Regularity: Monthly

Review Process: Double Blind

Time to Publication: 21 Days

Indexing catalog: IndexCopernicus ICV 2022: 88.03 | GoogleScholar | View more

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

License: Open Access by Journal of Biomedical Research & Environmental Sciences is licensed under a Creative Commons Attribution 4.0 International License. Based on a work at SciRes Literature LLC.

Manuscript should be submitted in Word Document (.doc or .docx) through Online Submission form or can be mailed to support@jelsciences.com

Vision: Journal of Biomedical Research & Environmental Sciences main aim is to enhance the importance of science and technology to the scientific community and also to provide an equal opportunity to seek and share ideas to all our researchers and scientists without any barriers to develop their career and helping in their development of discovering the world.
Abstract

Gastric Cancer (GC) presents a significant global health concern due to its high incidence and mortality rates. Despite advancements in medical treatments, drug resistance poses a major challenge in managing GC. Ferroptosis, a form of programmed cell death driven by iron-dependent lipid peroxidation, has emerged as a key contributor to treatment resistance in GC. The pivotal role of GPX4, a regulator of ferroptosis, has garnered considerable attention in cancer research. GPX4 synthesis and expression are subject to regulation at multiple levels, including transcription, translation, and posttranslational modifications. Ongoing development of pharmacological therapeutics targeting GPX4 aims to induce ferroptosis in cancer cells. This review provides an overview of the GPX4 pathway's involvement in GC, shedding light on the implications of ferroptosis induction in combatting cancer resilience. These findings emphasize the therapeutic potential of GPX4 in managing gastric cancer and other malignancies, presenting novel opportunities to address the challenges of treatment resistance.

Introduction

Gastric Cancer (GC) is the fifth most prevalent cancer and the fourth-leading cause of cancer-related mortality globally [1,2]. Various factors, including H. pylori infection, aging, smoking, alcohol consumption, diet, EBV infection and genetic predisposition, contribute to the risk of GC [3]. Clinical symptoms often manifest late, leading to advanced-stage diagnoses in most GC patients, limiting treatment options and resulting in a poor prognosis. Chemotherapy serves as the primary adjuvant therapy for advanced GC, but the development of chemotherapy resistance represents a critical challenge to its clinical effectiveness [4,5].

In recent years, ferroptosis, a distinctive form of non-apoptotic, programmed necroptotic cell death characterized by lipid peroxide accumulation, has garnered considerable attention in cancer research [6]. Increasing evidence implicates ferroptosis in treatment resistance, angiogenesis, metastasis, and tumor cell survival. Studies have demonstrated the selective eradication of tumor cells, hindering tumor progression and metastasis through ferroptosis. Recent research has illuminated the impact of ferroptosis on GC progression, and shown that therapies inducing ferroptosis can effectively eliminate GC or enhance
the effects of other therapies, signifying a promising treatment strategy [7–11].

Glutathione peroxidase 4 (GPX4), identified as a pivotal negative regulator of ferroptosis, holds significance in cancer research [12]. Belonging to the glutathione peroxidase family, GPX4 exhibits a high preference for lipid hydroperoxides, safeguarding cells against membrane lipid peroxidation and cell death (Figure 1)[13,14]. Inhibition or downregulation of GPX4 can lead to increased lipid peroxidation and ultimately trigger ferroptosis. GPX4’s potential for predicting prognosis, immunotherapy sensitivity, and immune infiltration in GC patients, as well as its role in selectively inducing ferroptotic death in various cancers, underscores its significance [15]. Given its distinctive involvement in ferroptosis and cancer development, GPX4 emerges as a promising target for cancer treatment and a potential prognostic biomarker [16,17]. Consequently, this review aims to delineate the regulatory mechanisms and functional roles of GPX4 in GC development, while also exploring its potential for overcoming drug resistance in cancer cells.

The involvement and regulation GPX4 in gastric cancer

GPX4 exhibits aberrant expression in various cancer types and is intricately linked to prognosis. It is significantly upregulated in hepatocellular carcinoma and colorectal carcinoma, while being downregulated in breast cancer and renal cell carcinoma compared to normal tissues. Additionally, in diffuse large B-cell lymphoma, lung adenocarcinoma, and esophageal cancer, GPX4 expression levels have emerged as a prognostic indicator [18–21]. Notably, elevated GPX4 expression has been recognized as a significant negative prognostic factor for GC patients [22].

Studies have revealed the diverse regulatory mechanisms of GPX4 in gastric cancer, including transcriptional, translational, and posttranslational modifications. For example, the β-catenin/TCF4 transcriptional complex directly binds to the

Figure 1 GPX4 acts as a negative regulator in ferroptosis. GPX4 is an enzyme that helps protect cells from oxidative damage by utilizing glutathione as a reducing agent to reduce lipid peroxidation products to their corresponding alcohols.
promoter region of GPX4, resulting in its upregulation and concurrent attenuation of ferroptosis in GC cells, thereby contributing to Cisplatin chemotherapy resistance [23]. Additionally, the high expression of cystatin SN (CST1) shields gastric cancer cells from ferroptosis by mitigating GPX4 ubiquitination modification through the recruitment of OTUB1, while CST1, increased in metastatic cancer, promotes migration and invasion [24]. In contrast, genetic inhibition of LTBP2 downregulates the NFE2L2 pathway in GC cells, leading to decreased GPX4 expression and induction of ferroptosis [25]. Furthermore, CircRHOT1 has been implicated in promoting GC progression and suppressing ferroptosis by recruiting KAT5 to promote the acetylation of the histone H3 protein subunit of the GPX4 gene, thereby initiating its transcription [26]. Moreover, the upregulation of GPX4, SLC7A11, and STAT3 in 5-FU-resistant GC cells underscores their role in drug resistance, with the inhibition of STAT3 inducing ferroptosis via transcriptional inhibition of GPX4 and SLC7A11 expression [27]. Additionally, the transcription factor sterol regulatory element–binding transcription factor 1 (SREBF1) has been identified as a potential target for overcoming drug resistance in GC, as its inhibition downregulates GPX4 expression, thereby inducing ferroptosis in multidrug-resistant GC cells [28].

**Targeting GPX4 in gastric therapy**

GPX4 has shown potential as a promising target for eradicating the therapy-resistant cancer by Inducing ferroptosis. Several compounds targeting GPX4 have been developed for GC treatment. For instance, the bioactive compound 6-thioguanine (6-TG) has demonstrated antitumor effects by inducing ferroptosis through blocking SLC7A11 activity and downregulating GPX4 expression [29]. Atranorin, a secondary metabolite of lichen, combined with superparamagnetic iron oxide NPs (atranorin@SPION), inhibits the expression of GPX4 and SLC7A11, thereby inducing ferroptosis in GC stem cells [30]. Similarly, herbal medicines such as Cirsium japonicum-mediated AuNPs (CJ-AuNPs) and the derivative of Jiyuan oridonin A have been shown to decrease GPX4 expression and induce ferroptosis in GC cells [31,32]. Apatinib, the derivative of Jiyuan oridonin A, has been demonstrated to target GPX4 and SLC7A11 expression by inhibiting the transcription factor STAT3-dependent GPX4 and SLC7A11 expression [27]. Ophiopogonin B (OP-B), extracted from Radix Ophiopogon japonicus, suppresses the proliferation of human GC cells by blocking the GPX4/xCT-dependent ferroptosis pathway [34]. These findings present opportunities for directing targeting GPX4 or inhibiting upstream transcription factors and signals to enhance sensitivity to ferroptosis–targeted therapies in GC cells.

**Conclusion and Perspective**

GPX4 expression has been recognized as a significant negative prognostic factor for GC patients. In this review, we summarized the regulatory mechanisms and functional roles of GPX4 in the development of gastric cancer, highlighted the importance of GPX4 as a negative regulator of ferroptosis in cancer research. Targeting GPX4 to induce ferroptosis holds promise as a strategy for overcoming therapy-resistant cancer. Further research is needed to gain a deeper understanding of the precise processes, efficacy, safety, and potential adverse effects associated with these strategies.

**Authors Contribution**

Conceptualization, M.Z. and P. L.; writing–original draft, M.Z.; writing–review and editing, J.X., S.Z. and P.L. All authors have read and agreed to the published version of the manuscript.

**References**


