**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 74044

**Manuscript Type:** LETTER TO THE EDITOR

**Inhibition of glutathione metabolism can limit the development of pancreatic cancer**

Cai PY *et* *al*. Glutathione metabolism affects pancreatic cancer

Pei-Yuan Cai, Mei-Lin Ma, Yang-Fen Zhang, Zi-Xuan Zhou, Yan Wang, Lian-Ping He, Wei Wang

**Pei-Yuan Cai, Wei Wang,** Department of Interventional Oncology, Municipal Hospital Affiliated to Taizhou University, Taizhou 318000, Zhejiang Province, China

**Mei-Lin Ma, Yang-Fen Zhang, Zi-Xuan Zhou, Yan Wang, Lian-Ping He,** School of Medicine, Taizhou University, Taizhou 318000, Zhejiang Province, China

**Author contributions:** Wang W and He LP contributed to conceptualization and formal analysis; Cai PY, Ma ML, Zhang YF, Wang Y, and Zhou ZX contributed to writing of the original draft, writing, reviewing, and editing; All authors participated in drafting the manuscript and have read, contributed to, and approved the final version of the manuscript.

**Corresponding author: Wei Wang, MD, Attending Doctor,** Department of Interventional Oncology, Municipal Hospital Affiliated to Taizhou University, No. 381-1 Zhongshan East Road, Jiaojiang District, Taizhou 318000, Zhejiang Province, China. westernfox000@163.com

**Received:** December 13, 2021

**Revised:** March 15, 2022

**Accepted:** April 27, 2022

**Published online:** May 26, 2022

**Abstract**

Pharmacological inhibitors of glutathione synthesis and circulation, such as buthionine-sulfoximine, inhibit glutathione metabolism. These drugs decrease the aggressiveness of pancreatic cancer, inhibit tumor stem cell survival, and reduce chemotherapy resistance. Nevertheless, buthionine-sulfoximine also decreases the content of glutathione in normal cells, disrupts the balance between reactive oxygen species and glutathione, and eventually induces cell apoptosis. Pancreatic cancer is usually diagnosed at an advanced stage and has a poor prognosis. Consequently, the use of biomarkers to screen high-risk patients can be an effective method.

**Key Words:** Cancer stem cells; Chemoresistance; Pancreatic cancer; Pancreatic ductal adenocarcinoma; Redox

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Cai PY, Ma ML, Zhang YF, Zhou ZX, Wang Y, He LP, Wang W. Inhibition of glutathione metabolism can limit the development of pancreatic cancer. *World J Stem Cells* 2022; 14(5): 362-364

**URL**: https://www.wjgnet.com/1948-0210/full/v14/i5/362.htm

**DOI**: https://dx.doi.org/10.4252/wjsc.v14.i5.362

**Core Tip:** To reduce side effects, pharmacological inhibitors of glutathione synthesis and circulation, such as buthionine-sulfoximine and 6-aminonicotinamide, can be assessed by *in vivo* models of pancreatic cancer. Evaluating the impact of different organs on metabolic processes and the invasiveness of cancer stem cells may provide new avenues for therapeutics targeting tumor metabolism.

**TO THE EDITOR**

We read a valuable article by Jagus *et al*[1] that highlights the role of glutathione (GSH) metabolism in pancreatic cancer stem cells (CSCs). The article provided valuable insight that a high GSH content is vital to retain the functionality of CSCs in terms of self-renewal and chemoresistance and provided a new direction for the treatment of pancreatic cancer. However, some issues require further discussion.

The balance between reactive oxygen species and GSH is essential for maintaining normal cell physiological activity[2]. Drugs used to interfere with the redox balance of the cell can cause adverse reactions and eventually lead to oxidative stress-induced cell death. Furthermore, imbalance in reactive oxygen species/GSH[3] can lead to oxidative stress, thereby promoting the occurrence and development of diseases. Buthionine-sulfoximine (BSO), a pharmacological inhibitor of GSH synthesis and circulation, can deplete intracellular GSH, thereby impairing CSC functions such as self-renewal and chemoresistance. However, the effects of BSO are limited, and it has no targeting effect on the regulation of cellular GSH. BSO reduces the content of GSH in normal cells and disrupts the redox balance of cells, thereby exacerbating the side effects of radiotherapy and chemotherapy. Further research is needed to explore the mechanism underlying the targeted metabolic vulnerability of aggressive cancer cell subpopulations characterized by extensive intratumoral heterogeneity. We suggest that the authors evaluate the therapeutic effects of pharmacological inhibitors of GSH synthesis and circulation such as BSO and 6-aminonicotinamide in a pancreatic cancer *in vivo* model.

Pancreatic cancer is usually detected at an advanced stage and eventually develops into a systemic disease[4]. Most treatment options are not effective, leading to a poor overall prognosis. Optimizing the adjuvant and neoadjuvant methods of conventional chemotherapy and radiotherapy[5] is of great significance to prolong the median survival of patients with pancreatic cancer. However, there are few long-term survivors of pancreatic cancer. In addition, the prognostic impact and quality of life of pancreatic cancer should be fully considered. Therefore, early detection of tumors, such as finding high-risk patients through new biomarkers and screening tools, and early preventive treatment may be more effective. We recommend that the authors monitor the GSH content of pancreatic CSCs and the expression of multiple genes in the GSH metabolic pathway. These can be used as biomarkers of pancreatic cancer for the early screening of high-risk patients, which may open up new possibilities for treatments targeting tumor metabolism.

Pancreatic ductal adenocarcinoma[6] metastasizes to distant organs, which is the main cause of death. CSCs and cell metabolism play a key role in metastasis. There is a strong link between different CSC subtypes and organ-specific colonization[7], and different CSCs adapt to the unique metabolic characteristics of organ metastasis. Pancreatic cancer can easily develop into a systemic disease. Therefore, the authors should consider the influence of different organs on the metabolic programming of CSCs and increase the samples of pancreatic ductal adenocarcinoma cells grown in different organ mimic models to improve the credibility and reliability of the article.

**REFERENCES**

1 **Jagust P**, Alcalá S, Sainz Jr B, Heeschen C, Sancho P. Glutathione metabolism is essential for self-renewal and chemoresistance of pancreatic cancer stem cells. *World J Stem Cells* 2020; **12**: 1410-1428 [PMID: 33312407 DOI: 10.4252/wjsc.v12.i11.1410]

2 **Khan M**, Li T, Ahmad Khan MK, Rasul A, Nawaz F, Sun M, Zheng Y, Ma T. Alantolactone induces apoptosis in HepG2 cells through GSH depletion, inhibition of STAT3 activation, and mitochondrial dysfunction. *Biomed Res Int* 2013; **2013**: 719858 [PMID: 23533997 DOI: 10.1155/2013/719858]

3 **Liu T**, Sun L, Zhang Y, Wang Y, Zheng J. Imbalanced GSH/ROS and sequential cell death. *J Biochem Mol Toxicol* 2022; **36**: e22942 [PMID: 34725879 DOI: 10.1002/jbt.22942]

4 **Ansari D**, Tingstedt B, Andersson B, Holmquist F, Sturesson C, Williamsson C, Sasor A, Borg D, Bauden M, Andersson R. Pancreatic cancer: yesterday, today and tomorrow. *Future Oncol* 2016; **12**: 1929-1946 [PMID: 27246628 DOI: 10.2217/fon-2016-0010]

5 **Torphy RJ**, Fujiwara Y, Schulick RD. Pancreatic cancer treatment: better, but a long way to go. *Surg Today* 2020; **50**: 1117-1125 [PMID: 32474642 DOI: 10.1007/s00595-020-02028-0]

6 **Huang P**, Wang CY, Gou SM, Wu HS, Liu T, Xiong JX. Isolation and biological analysis of tumor stem cells from pancreatic adenocarcinoma. *World J Gastroenterol* 2008; **14**: 3903-3907 [PMID: 18609717 DOI: 10.3748/wjg.14.3903]

7 **Nimmakayala RK**, Leon F, Rachagani S, Rauth S, Nallasamy P, Marimuthu S, Shailendra GK, Chhonker YS, Chugh S, Chirravuri R, Gupta R, Mallya K, Prajapati DR, Lele SM, C Caffrey T, L Grem J, Grandgenett PM, Hollingsworth MA, Murry DJ, Batra SK, Ponnusamy MP. Metabolic programming of distinct cancer stem cells promotes metastasis of pancreatic ductal adenocarcinoma. *Oncogene* 2021; **40**: 215-231 [PMID: 33110235 DOI: 10.1038/s41388-020-01518-2]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 13, 2021

**First decision:** March 13, 2022

**Article in press:** April 27, 2022

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Imai Y, Japan; Sahoo J, India; Yoshizawa T, Japan **S-Editor:** Ma YJ **L-Editor:** Filipodia **P-Editor:** Ma YJ



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**