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LETTER TO THE EDITOR

Inhibition of glutathione metabolism can limit the development of pancreatic cancer

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

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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

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.

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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.

FOOTNOTES

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.

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