Commentary
Volume 09:01, 2024

Journal of Molecular Histology and Medical Physiology

ISSN: 2684-494X

Open Access

Ferroptosis: A New Target for Treatment of Bladder Cancer

Zhang Jah*

Department of Medicine, Sun Yat-sen University, Shenzhen, China

Introduction

Bladder cancer is a significant global health concern, with a high recurrence rate and limited treatment options. In recent years, the understanding of cancer biology has evolved, and emerging research has shed light on new therapeutic approaches. One of the most promising avenues is the study of ferroptosis, a unique form of regulated cell death that is characterized by iron-dependent lipid peroxidation. This article explores the role of ferroptosis in bladder cancer, the mechanisms involved, and the potential for targeting this pathway as a novel treatment strategy. We will delve into the implications of ferroptosis induction, its interaction with conventional therapies, and the challenges that need to be overcome for the successful integration of ferroptosis-targeted therapies in the clinical management of bladder cancer. Bladder cancer is a common malignancy, ranking among the top ten most prevalent cancers worldwide. According to the World Cancer Research Fund, there were over 500,000 new cases and 200,000 deaths attributed to bladder cancer in 2020 alone. The management of bladder cancer presents numerous challenges, given its high recurrence rate and limited treatment options. Surgery and traditional chemotherapy, while valuable, often result in incomplete remission and significant side effects. Therefore, it is crucial to explore novel therapeutic approaches for bladder cancer [1-3].

In recent years, there has been growing interest in ferroptosis as a potential target for cancer therapy. Ferroptosis is a unique form of programmed cell death characterized by the iron-dependent accumulation of lipid peroxides and the subsequent lethal damage to cell membranes. This process is distinct from apoptosis, necrosis, and autophagy, which are other forms of cell death that have been widely studied in the context of cancer. Understanding the role of ferroptosis in bladder cancer and exploring its therapeutic potential offers a fresh perspective on the treatment of this disease. Ferroptosis was first described in 2012 as a distinct form of regulated cell death, different from apoptosis and necrosis. The term "ferroptosis" is derived from the Latin word "ferrum," which means iron, and the Greek word "ptosis," which means falling. The central characteristic of ferroptosis is the iron-dependent accumulation of lipid peroxides, particularly in phospholipid membranes. This accumulation leads to oxidative damage and cell death.

Intracellular iron levels play a crucial role in ferroptosis. Iron is necessary for the generation of Reactive Oxygen Species (ROS) through the Fenton reaction, which contributes to lipid peroxidation. GSH is an antioxidant that helps protect cells from oxidative stress. In ferroptosis, GSH levels are reduced, impairing the cell's ability to neutralize ROS and lipid peroxides. Accumulation of lipid peroxides is a hallmark of ferroptosis. This process is initiated by the action of Lipoxygenases (LOX) on polyunsaturated fatty acids within cell membranes. System Xc- is a membrane transporter that imports cystine, an amino acid required for GSH synthesis. Inhibition of System Xc- reduces intracellular cystine levels, leading to GSH depletion and increased susceptibility to ferroptosis., Glutathione Peroxidase 4 (GPX4) is an enzyme that protects against lipid peroxidation. In ferroptosis, GPX4 activity is reduced, leaving cells vulnerable to oxidative damage.

Bladder cancer is a heterogeneous disease with multiple subtypes, including non-muscle-invasive and muscle-invasive tumors. Understanding the role of ferroptosis in bladder cancer is crucial to explore its potential as a therapeutic target. Several recent studies have provided insights into the involvement of ferroptosis in bladder cancer progression. In bladder cancer, ferroptosis resistance has been observed, contributing to tumor growth and therapy resistance. This resistance is often associated with elevated levels of anti-ferroptotic proteins, such as GPX4 and SLC7A11 (the subunit of System Xc-), which counteract the induction of ferroptosis. This resistance may explain the limited efficacy of traditional chemotherapy regimens in some patients.

Description

Studies have shown that lipid peroxidation and the accumulation of lipid peroxides are associated with bladder cancer progression. Increased levels of Lipoxygenases (LOX) have been reported in bladder cancer tissues, which promote lipid peroxidation and potentially contribute to ferroptosis induction. However, this process may be insufficient to induce ferroptosis due to the aforementioned resistance mechanisms. Iron metabolism is often dysregulated in cancer cells, and this is also true for bladder cancer. Intracellular iron levels may be elevated in bladder cancer, contributing to the oxidative stress and lipid peroxidation associated with ferroptosis. Targeting iron metabolism could potentially sensitize bladder cancer cells to ferroptosis induction [4].

Recent research has highlighted the connection between ferroptosis and immune evasion in bladder cancer. Immune cells play a critical role in recognizing and eliminating cancer cells. Ferroptotic cancer cells release Damage-Associated Molecular Patterns (DAMPs), which can enhance immune responses. However, the interaction between ferroptosis and immune responses in bladder cancer is complex and requires further investigation. The involvement of ferroptosis in bladder cancer opens up new avenues for therapeutic intervention. Targeting ferroptosis represents a novel approach that could complement existing treatment strategies. Inhibiting GPX4, the enzyme responsible for protecting cells from lipid peroxidation, is a promising approach to induce ferroptosis in bladder cancer. Several small molecules and compounds that target GPX4 have been developed and are under investigation. These compounds can sensitize cancer cells to ferroptosis, potentially enhancing the effectiveness of chemotherapy. System Xc- is a key player in maintaining cellular redox balance. Inhibiting System Xc- can deplete intracellular cystine, leading to GSH depletion and increased vulnerability to ferroptosis. Combining System Xc- inhibitors with conventional chemotherapy could enhance the response of bladder cancer cells to treatment.

Given the dysregulation of iron metabolism in bladder cancer, iron chelation therapy may be a viable approach to induce ferroptosis. Iron chelators can sequester excess intracellular iron, reducing its availability for the Fenton reaction and subsequent lipid peroxidation. This strategy may be particularly relevant for patients with iron-overloaded tumors. Stimulating lipid peroxidation through the use of LOX activators or inhibitors of lipid repair pathways can increase the accumulation of lipid peroxides, promoting ferroptosis in bladder cancer cells. However, these approaches must be carefully tailored to minimize off-target effects on normal cells [5].

Conclusion

Combining ferroptosis-inducing agents with conventional chemotherapy

***Address for Correspondence:** Zhang Jah, Department of Medicine, Sun Yat-sen University, Shenzhen, China; E-mail: zhangjah@gmail.com*

Received: 13 December 2023, Manuscript No. jmhmp-23-117514; **Editor Assigned:** 15 December 2023, PreQC No. P-117514; **Reviewed:** 27 December 2023, QC No. Q-117514; **Revised:** 01 January 2023, Manuscript No. R-117514; **Published:** 08 January 2024, DOI: 10.37421/2684-494X.2024.9.110

or immunotherapy could represent a powerful approach to enhance the treatment of bladder cancer. This synergy may overcome resistance mechanisms and improve overall therapeutic outcomes. Ferroptosis-inducing agents can have off-target effects on normal cells, leading to unintended damage. Achieving specificity for cancer cells while sparing healthy tissues is a significant challenge that researchers need to address. Understanding and circumventing the resistance mechanisms that bladder cancer cells employ to evade ferroptosis is critical. Identifying predictive biomarkers of ferroptosis responsiveness is essential for patient stratification and personalized treatment. Optimizing combination therapies that incorporate ferroptosis inducers with existing treatments or immunotherapies is a complex task. Dosage, timing, and sequencing are all critical factors that need to be carefully considered. The interplay between ferroptosis and the immune system in bladder cancer is not yet fully understood. Harnessing this interaction for therapeutic benefit requires further research. Translating ferroptosis-based therapies from preclinical research to clinical practice is a significant undertaking. Rigorous clinical trials are needed to validate the safety and efficacy of these approaches in human patients. Ferroptosis represents a novel and promising approach for the treatment of bladder cancer. Understanding the role of ferroptosis in bladder cancer progression and developing targeted strategies to induce ferroptosis can open up new avenues for therapeutic intervention. Overcoming resistance mechanisms, optimizing combination therapies, and translating preclinical findings into clinical practice are the next steps in harnessing the potential of ferroptosis-based treatments for bladder cancer. As our understanding of ferroptosis continues to evolve, it offers hope for more effective and less toxic treatment options for bladder cancer patients in the future.

Acknowledgement

None.

Conflict of Interest

There is no conflict of interest by author.

References

1. Sato, Hideyo, Ayako Shiiya, Mayumi Kimata and Kanako Maebara, et al. "Redox imbalance in cystine/glutamate transporter-deficient mice." *J Biol Chem* 280 (2005): 37423-37429.
2. Yang, Wan Seok and Brent R. Stockwell. "Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-ras-harboring cancer cells." *Chem Biol* 15 (2008): 234-245.
3. Nyquist, S. E., Rita Barr and D. James Morré. "Ubiquinone from rat liver golgi apparatus fractions." *Biochim Biophys Acta* 208 (1970): 532-534.
4. Nemeth, Elizabeta, Marie S. Tuttle, Julie Powelson and Michael B. Vaughn, et al. "Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization." *science* 306 (2004): 2090-2093.
5. Shen, Liliang, Junfeng Zhang, Zongtai Zheng and Fuhan Yang, et al. "PHGDH inhibits ferroptosis and promotes malignant progression by upregulating SLC7A11 in bladder cancer." *Int J Biol Sci*18 (2022): 5459-5474.

How to cite this article: Jah, Zhang. "Ferroptosis: A New Target for Treatment of Bladder Cancer." *J Mol Hist Med Phys* 9 (2024): 110.