COMMENTARY ARTICLE

Hematological malignancies and ferroptosis: A possible link to aberrant tumor metabolism

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ABSTRACT

Ferroptosis, a novel kind of controlled cell death, has properties that clearly distinguish it from apoptosis, autophagy, and necroptosis. Targeting ferroptosis is becoming recognized as a potentially innovative technique in anti-tumor treatment, particularly for aggressive cancers resistant to chemotherapy. Almost all forms of cancer cells rely on irregular metabolic activities to engage in a vicious cycle, providing the opportunity to interfere with underlying metabolic preferences and impair malignant cells by causing ferroptosis. In this context, we provide an overview of putative relationships between ferroptosis and aberrant tumor metabolism, with a specific emphasis on systematic studies in haematological malignancies.

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Hematological cancer is a group of malignant neoplasms that result from the abnormal differentiation and immortal proliferation of hematopoietic cells, resulting in biological organ malfunction and final stage. Acute Myeloid Leukaemia (AML), Chronic Myeloid Leukaemia (CML), acute lymphoblastic leukaemia (ALL), Chronic Lymphocytic Leukaemia (CLL), multiple myeloma (MM), and Non-Hodgkin Lymphoma (NHL) are the most prevalent haematological cancers. Patients gain universally from apoptosis-targeting chemotherapy, although the majority of them will eventually experience recurrence. Furthermore, a subset of patients is fundamentally resistant to conventional therapies. As a result, developing new anti-tumor strategies is critical. It is a possible technique to investigate how to remove cancer cells by various modes of cell death in order to improve the curative impact. Apoptosis, necroptosis, autophagy, ferroptosis, and pyroptosis are examples of well-known controlled cell death (RCD) processes. Among them, ferroptosis is a growingly appealing cell death process characterised by iron dependency and the buildup of lipid peroxides. A number of studies found that these ferroptosis properties varied from other forms of RCD, indicating that targeting ferroptosis might be a novel method in anti-tumor treatment. As a result, Ferroptosis Inducers (FINs) are predicted to limit the lifespan of malignant cells as striking weapons. To upregulate metabolic pathways and fulfil massive energy requirements in malignant cells, abundant nutrients are continually acquired by metabolic reprogramming.

However, in other circumstances, metabolic plasticity that favors cancer cells can be turned into successful cancer therapies. Because FINs are classified as a class of drugs that target metabolic transformation. Hematological malignancies, unlike solid tumors, cannot be removed surgically and must instead be treated with chemotherapy and targeted therapy. However, the unique metabolic pattern of tumor cells, as well as the potent influence of the microenvironment on immunosuppression, may render traditional therapy strategies ineffective. Further research is needed to determine if the features of haematological cancers have a role in causing the distinct vulnerability to ferroptosis. All of the above points to a potential future in researching the susceptibility shown in tumoral metabolic remodelling. We review systematic studies of ferroptosis and associated metabolic processes in haematological malignancy and analyse their possible connections in an attempt to give more insights. Primarily, erastin killed a non-APL AML cell line with NRAS Q61L mutations by a combination of cell death processes, ferroptosis and necroptosis. A modest dosage of erastin, on the other hand, sensitised AML cells to chemotherapeutic drugs (cytarabine, doxorubicin) irrespective of RAS signalling. Following the discovery of these

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events, it is possible that the plausible regulating mechanism will be uncovered. High-mobility group box (HMGB1) was shown to be triggered by erastin and directed into the cytoplasm from the nucleus in AML cells, where it enhanced intracellular iron levels and malondialdehyde formation via the RAS-JNK/p38 pathway. In Burkitt lymphoma (BL), ferroptosis was triggered with an apparent ER stress response, which increased ferroptosis rather than apoptosis. However, investigations with only one cell line restrict the probative value in displaying putative functions or regulation of ferroptosis; further research is required. Furthermore, lipoxygenases (LOXs) were shown to be responsible for the production of peroxides by oxidising unsaturated fatty acids and pan-inhibitors or specific 12/15-LOX inhibitors protected ALL cells from RSL3-induced ferroptosis. This discovery is similar to the research on chronic myeloid leukaemia (CML) cells. The mechanism of ferroptosis was alluded to by lipid metabolism enzymes Acyl-CoA synthetase long-chain family member 4 (ACSL4) or lysophosphatidylcholine acyltransferases 3 (LPCAT3) that triggered lipid reprogramming. To summarise, the implementation of lipid metabolism in ferroptosis with reliance on lipid remodelling communicators is unarguable. Regrettably, there is now no evidence of a unique relationship between ACSL4 and LPCAT3, a common ferroptosis regulator for cancer, and haematological malignancy. Recently, it was discovered that epigenetic factors regulate ferroptosis. CircKDM4C, a non-coding RNA that promotes ferroptosis in AML cells, boosted wild-type P53 expression by competitively deleting another non-coding RNA, hsa-let-7b-5p.

In addition to the traditional FINs described above, several additional small chemical agents have been discovered to cause ferroptosis in haematological cancer cells. In particular, dihydroartemisinin (DHA) induced ferritin breakdown in AML via activating autophagy, resulting in LIP over-loading and massively ferroptotic cell death. Simultaneously, typhaneoside (TYP), a key flavonoid in Pollen Typhae extract, clearly activated autophagy in AML by speeding AMPK signalling activation, helping ferroptosis with ferritin breakdown, and increasing ROS buildup. Furthermore, artesunate (ART), a commonly used antimalarial drug, induced a mix of cell death (caspase-dependent apoptosis, ROS-dependent ferroptosis, and necroptosis) in adult T-cell leukemia/lymphoma (ATLL) cells. In addition, T-cells infected with human T-cell leukaemia virus type 1 (HTLV-1) were substantially more sensitive to ART-induced growth suppression than uninfected T cells. Interestingly, fingolimod (FTY720), a new immunosuppressant, reduced the expression of both GPX4 and SLC7A11 in MM cells, exerting a substantial inhibitory effect on MM cells via autophagy and ferroptosis.

APR-246, a promising new medication targeting p53-mutated proteins, was recently shown to cause cell death in a p53-independent way. Early cytotoxicity was seen in AML cells following exposure to APR-246, which was later alleviated by iron chelators, lipophilic antioxidants, and inhibitors of lipid peroxidation, satisfying the description of ferroptosis. Only by increasing cystine absorption capacity can AML cells detoxify lipid peroxides and preserve redox equilibrium in the face of APR-246 damage, indicating that cystine metabolism regulators may be an important predictor of susceptibility to APR-246. Furthermore, APR-246 had an extremely synergistic impact when combined with pharmacological treatments or genetic knockdown of SLC7A11 or GPX4. Finally, in addition to erastin and RSL3, new compounds PK-3 and CIL56 promoted ferroptosis in CML cells via the underappreciated role of lipid metabolism genes.

Ferroptosis, which differs from other forms of RCD, is predicted to be a novel anti-tumor therapeutic method. Metabolic reprogramming is one of the most unusual features of tumour cells, but it also has a significant influence on ferroptosis. Thus, researching aberrant metabolic patterns associated with ferroptosis or diagnostic procedures aids us in understanding ferroptosis-regulated pathways. We discuss ferroptosis-related metabolic problems and the underlying possible connections with ferroptosis in haematological malignancies, which calls for greater research. A thorough understanding of the theories presented above contributes to a promising future.