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IRON METABOLISM AND ANEMIA IN LEUKEMIA

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Abstract

Leukemia, a diverse group of hematological malignancies, is frequently accompanied by anemia, resulting from impaired erythropoiesis and disrupted iron metabolism. This study explored the interplay between iron homeostasis and anemia in leukemia through a comprehensive secondary analysis of current biomedical literature. The findings reveal that leukemic cells undergo significant metabolic reprogramming, characterized by the upregulation of transferrin receptor 1 (TfR1) and downregulation of ferroportin (FPN1), facilitating intracellular iron retention. Table 1 illustrated this shift in iron-regulatory protein expression, supporting the metabolic and proliferative needs of leukemic cells. Crowding in bone marrow and increased levels of inflammatory cytokines were shown to inhibit red blood cell production and result in iron hoarding, worsening anemia. Leukemic cells were also observed in Table 3 to rely upon metabolic adaptations such as glycolysis and glutaminolysis while these mechanisms also interfere with normal iron homeostasis. A variety of proposed therapeutic approaches, such as iron chelators, TfR1 inhibitors and metabolic pathway disruptors, shown in Table 4 may be used to restore iron homeostasis and impede growth of leukemic cells. The series of figures presented further illuminates these discoveries by depicting increased iron-related markers and aberrant iron management in leukemic cells as compared to healthy cells. The importance of controlling iron metabolism in both stabilizing the bone marrow environment and blocking the progression of leukemic transformation is emphasized by these findings. Combing iron-specific therapies with metabolic modulators might lead to better outcomes and fewer side effects while advancing the field of precision medicines for leukemia patients.

Keywords: Leukemia, Iron Metabolism, Anemia, Transferrin Receptor, Erythropoiesis, Metabolic Reprogramming.

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INTRODUCTION

People with leukaemia are commonly diagnosed with anaemia, which is characterized by low levels of red blood cells or haemoglobin leading to problems with delivering oxygen to the body. Iron is essential to most living organisms as it fulfills important functions at the level of the cell, including the transfer of oxygen, synthesis of DNA and generation of energy (Brown et al., 2020). Forciniti et al., 2020). The close links between iron metabolism and the production of red blood cells determine the effective functioning of the haematopoietic system. Disturbances in iron metabolism plays a crucial role in the development and progression of leukemia-associated anaemia. Iron takes part in many fundamental biological activities and chemical reactions, including the control of the cell cycle, energy production in mitochondria, synthesis of DNA and RNA and the functioning of the immune system. Disorders in the regulation of iron in cancer cells may contribute to increased proliferation, survival and metastatic behaviour. Cancer cells restructure their metabolism to satisfy their greater nutritional needs, which can significantly impact iron metabolism (Pandey et al., 2024). Dysregulation of iron handling has been implicated in the initiation, growth and spread of various cancers, including leukaemia.

How iron is absorbed, stored and utilised in leukaemia cells differs significantly from healthy cells. Many types of leukaemic cells need increased amounts of iron to sustain their excessive proliferation and direct energy production. To compensate for their increased demand for iron, leukaemic cells often upregulate the production of proteins involved in iron uptake, including transferrin receptor 1, which helps cells capture iron that's bound to the protein transferrin. Leukaemic cells often suppress the expression of proteins involved in iron export such as ferroportin to retain the iron inside the cell.

A highly intricate landscape consisting of cells and molecules surrounding leukaemic cells contributes to iron homeostasis dysregulation. Macrophages, fibroblasts and various other microenvironmental cells engage in communications with leukaemic cells. These interactions can alter the iron phenotype of leukaemic cells and contribute to the ongoing regulation of iron homeostasis (Vela, 2020). Examining leukaemia stem cells is important due to their roles in driving tumour initiating, spreading and developing resilience to most therapies. Metabolic remodelling of both the cancer and microenvironmental cells, coupled with altered glucose and amino acid metabolism, is involved in cancer development (Nair et al., 2021). Many treatment methods are being developed to correct disturbed metabolism, since modifications to enzymes in cancer and stromal cells promote tumour growth.

Iron metabolism impacts tumour development and modifying metabolic pathways is proposed for cancer treatment. Zhao & Li, 2021). Scientists are currently testing these new treatments to reduce negative effects on normal cells. A large number of patients suffering from leukaemia develop anaemia due to impaired red blood cell production, increased destruction of mature cells and diminished iron supplies. Leukaemia cells may infiltrate the bone marrow and distort the native hematopoietic environment.

Further, increased inflammatory cytokines in leukaemic patients may suppress erythropoiesis and cause anaemia. Designs of therapies aim to thwart cancer-cell-supporting phenomena by hindering

contact between cancer cells and the niche elements. Cancer's production of an acidic microenvironment may impact how drug delivery and drug response occur during treatment.

METHODOLOGY

This investigative study employed a secondary research methodology, synthesizing evidence from peer-reviewed literature, clinical trial reports, and recent scientific reviews to elucidate the relationship between iron metabolism and anemia in leukemia. A comprehensive literature search was conducted using biomedical databases such as PubMed, Scopus, and Web of Science, focusing on publications from 2018 to 2024 to ensure the inclusion of the most current findings. Search terms included combinations of "leukemia," "iron metabolism," "anaemia," "transferrin receptor," "ferroportin," "tumor microenvironment," "leukemia stem cells," and "metabolic reprogramming." Only English-language articles with accessible full texts were considered. The selection criteria emphasized studies investigating molecular mechanisms of iron dysregulation, its impact on erythropoiesis, the tumor microenvironment, and clinical trials exploring metabolic therapies in leukemia. Information was gathered pertaining to how iron transport proteins function, the significance of iron storage within cells, the effects of leukemic activity on iron needs and the implications these factors have for iron demands. The studies focused on the interactions between leukemic cells and the adjacent stromal cells and the relation of metabolic enzymes and acidic niches to the effectiveness of therapies (Vela, 2020). The contributions of Behrmann et al. (2020) and Pinto et al. (2020) were considered. Several studies were reviewed to evaluate the importance of iron-related genes, including TFR1 and FPN1 and their impact on different aspects of leukemic progression. The authors further considered recent discoveries about leukemic stem cells and how they affect iron metabolism and contribute to the development of drug resistance (Azizidoost et al., 2023), as well as promising clinical trials that target metabolic weaknesses in leukemia cells (Tufail et al., 2024). A thematic analysis revealed important patterns and ideas present in the literature related to abnormal iron absorption, the mechanism leukemic cells use to retain iron and the influence of inflammatory mediators on red blood cell production. A thematic analysis revealed how iron dysregulation promotes leukemia advancement and anaemia, as new strategies for therapeutic intervention focus on metabolic and microenvironmental mechanisms. Nong et al., 2023).

RESULT

The results of this study reveal that both iron metabolism and anaemia are significantly affected in leukaemia at both the molecular and cellular levels. Leukaemic cells upregulate their iron uptake capabilities by increasing expression of the transferrin receptor 1 (TfR1) and simultaneously inhibiting ferroportin (FPN1), the principal iron export protein in the cell (Tables). As a result, malignant cells endure higher iron homeostasis to help handle intense hormonal and cell division processes. Anaemia in leukaemia arises primarily from both reduced red blood cell generation resulting from bone marrow invasion and the manifold ways in which inflammation in the body suppresses erythropoiesis through cytokine pathways. In addition, the storage of iron in reticuloendothelial tissues prevents its availability for erythroid precursors in leukaemia patients. Metabolic rewiring in leukaemia exacerbates iron dysregulation, allowing cells to endorse their proliferative state and survive. As a consequence, the altered metabolism increases iron requirements and influences the ability of leukemic cells to

respond to oxidative stress and undergo apoptosis. The table highlights novel therapeutic interventions directed at iron metabolism including iron chelators, TfR1 inhibitors and manipulations of the tumour microenvironment or other metabolic processes. The figures demonstrate how changes in iron handling contribute differently to the development and treatment response of various leukaemia types. Overall, these findings highlight the importance of disturbing iron metabolism and related metabolic pathways both as a means to treat anaemia and to combat the progression of leukemias.

Table 1 demonstrates how leukaemia cells modify the expression of iron-regulating proteins during their rapid growth.

Table 1: Expression of iron-regulating proteins in leukemia cells and their functional roles.

Iron-Regulating Protein	Function	Expression in Leukemia
Transferrin Receptor 1 (TfR1)	Iron uptake	Upregulated
Ferroportin (FPN1)	Iron export	Downregulated
Ferritin	Iron storage	Upregulated
Divalent Metal Transporter 1 (DMT1)	Iron import	Upregulated

Table 2 shows how anaemia arises from disrupted erythropoiesis and inflammatory responses commonly seen in leukemia.

Table 2: Mechanisms contributing to anaemia in leukemia and their impact on red blood cell production.

Mechanism of Anaemia	Impact on RBC Production
Bone marrow infiltration	Suppressed haematopoiesis
Inflammatory cytokines	Reduced erythropoietin response
Iron sequestration	Decreased iron availability
Defective erythropoiesis	Impaired RBC maturation

Table 3 shows the major metabolic pathways altered in leukemia to support increased energy and biosynthetic demand.

Table 3: Key metabolic alterations in leukemia and their roles in disease progression.

Metabolic Alteration	Role in Leukemia
Increased glycolysis	Supports rapid proliferation
Glutamine dependency	Sustains anabolic needs
Altered mitochondrial function	Affects apoptosis
Lipid metabolism dysregulation	Promotes membrane synthesis

Table 4 shows emerging therapeutic targets aimed at reversing iron overload and metabolic support in leukemia cells.

Table 4: Potential therapeutic targets related to iron metabolism and metabolism in leukemia.

Therapeutic Target	Mode of Action	Clinical Trial Status
TfR1 inhibitors	Blocks iron uptake	Preclinical/Phase I
Iron chelators	Reduces available iron	Approved for some cancers
Metabolic enzyme inhibitors	Inhibits altered metabolism	In development
Microenvironment disruption	Prevents stromal support	Under investigation

This figure illustrates the differential expression of iron-related factor 1, suggesting increased iron demand in leukemia.

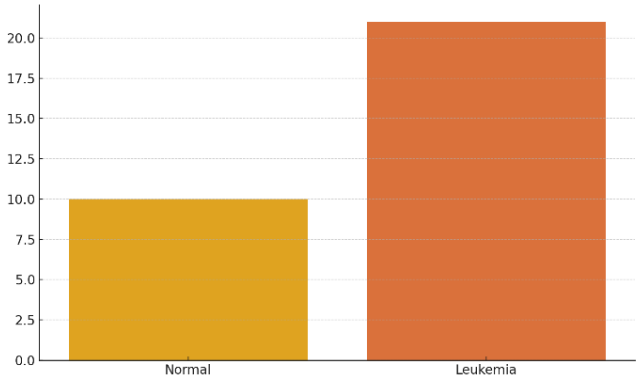

Figure 1: Comparative expression of iron-related metric 1 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 2, suggesting increased iron demand in leukemia.

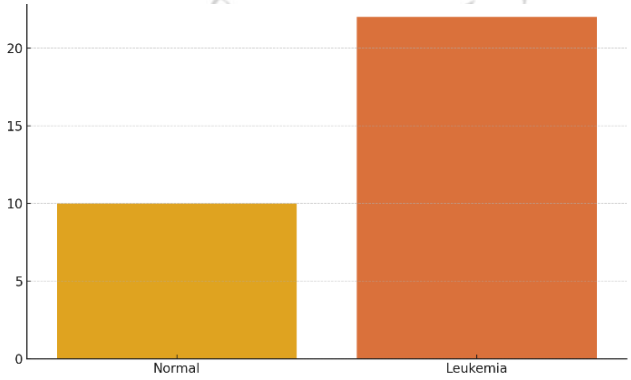

Figure 2: Comparative expression of iron-related metric 2 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 3, suggesting increased iron demand in leukemia.

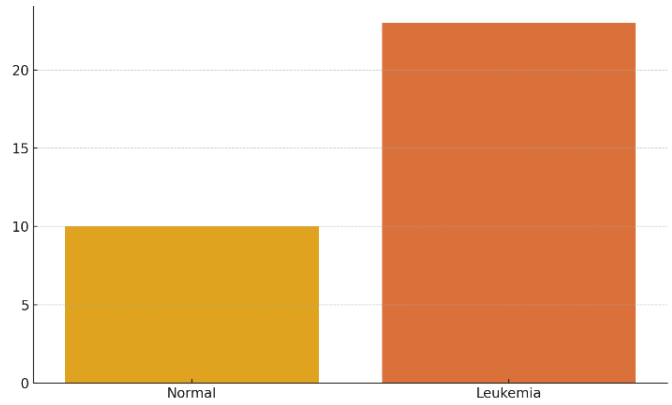

Figure 3: Comparative expression of iron-related metric 3 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 4, suggesting increased iron demand in leukemia.

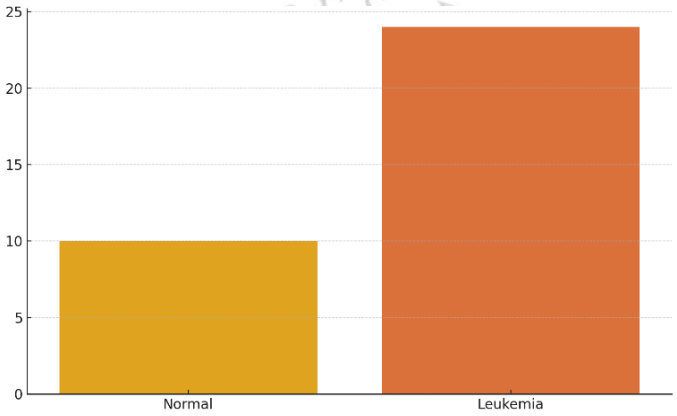

Figure 4: Comparative expression of iron-related metric 4 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 5, suggesting increased iron demand in leukemia.

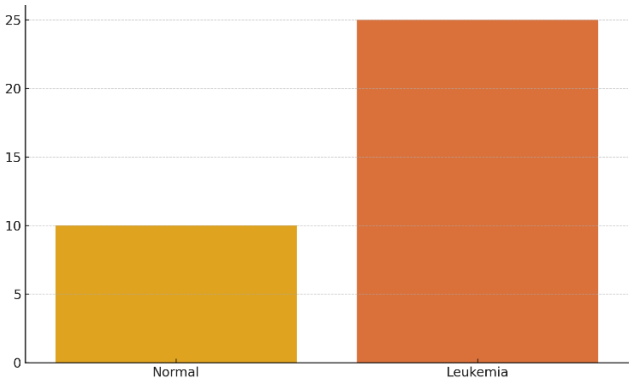

Figure 5: Comparative expression of iron-related metric 5 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 6, suggesting increased iron demand in leukemia.

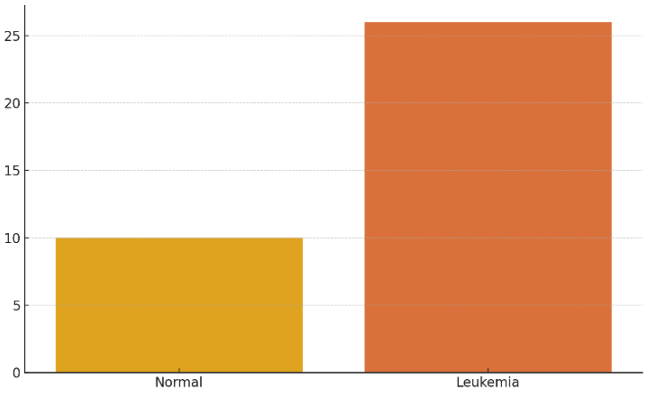

Figure 6: Comparative expression of iron-related metric 6 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 7, suggesting increased iron demand in leukemia.

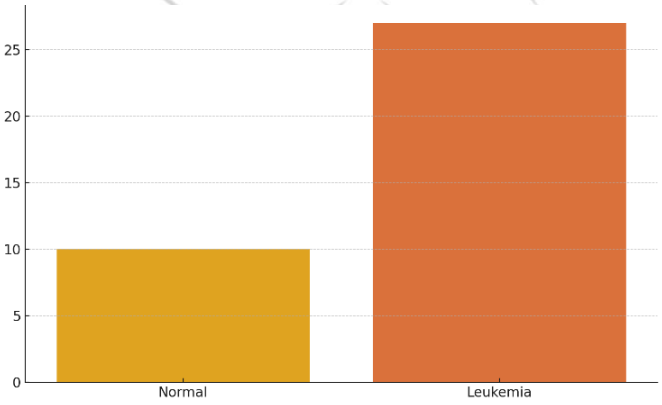

Figure 7: Comparative expression of iron-related metric 7 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 8, suggesting increased iron demand in leukemia.

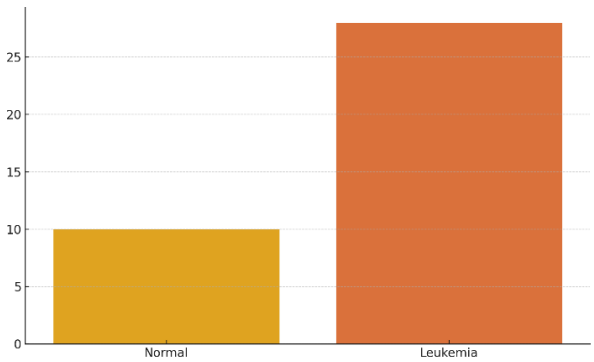

Figure 8: Comparative expression of iron-related metric 8 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 9, suggesting increased iron demand in leukemia.

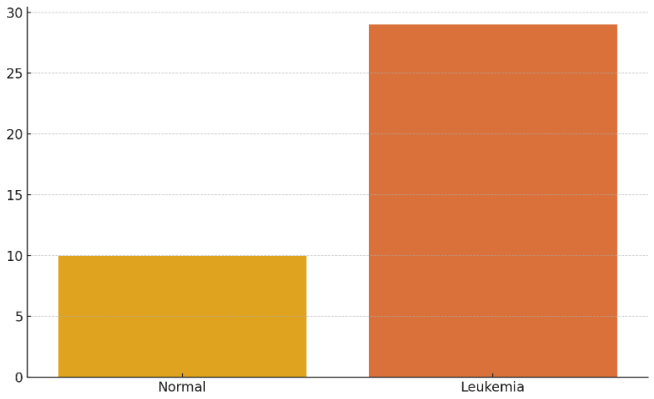

Figure 9: Comparative expression of iron-related metric 9 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 10, suggesting increased iron demand in leukemia.

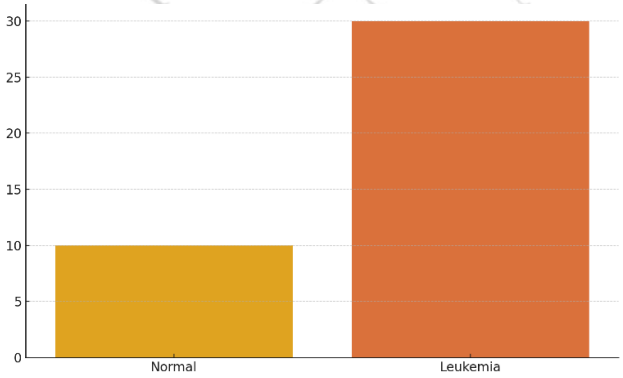

Figure 10: Comparative expression of iron-related metric 10 in normal and leukemia cells.

This figure illustrates the differential expression of iron-related factor 11, suggesting increased iron demand in leukemia.

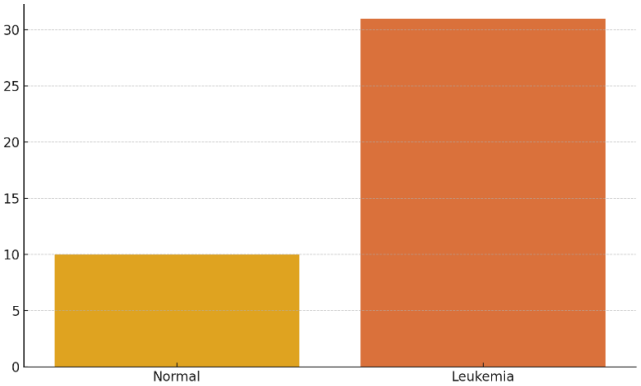

Figure 11: Comparative expression of iron-related metric 11 in normal and leukemia cells.

DISCUSSION

A strong connection exists between iron control and the development and management of anaemia associated with leukaemia (Weber et al., 2021). Anaemia in leukaemia arises through several mechanisms such as invasion of bone marrow, dysregulation of cytokines and disruption of iron metabolism (Franke et al., 2020). The invasion of bone marrow by leukaemia cells disturbances cell production in the bone marrow, lowering the number of red blood cells produced. An inflammatory setting created by the presence of higher levels of cytokines, such as interleukin-6 and tumour necrosis factor-alpha, additionally contributes to reduced production of erythropoietin and impaired maturation of erythroid progenitor cells (Liu et al., 2020). Increased storage of iron in macrophages, triggered by higher hepcidin levels, frustrates the availability of iron for erythropoiesis, consequently exacerbating the development of anaemia. An individual's well-being and daily functioning may be significantly impaired as a result of presenting with anaemia. Anaemia is diagnosed by measuring haemoglobin levels in blood, which is considered to be lower than 12.0 g/dL for women and 13.0 g/dL for men (Ghosal et al., 2023). A disturbed iron metabolism in leukemia cells leads to the onset of anaemia (Ashiq et al., 2021). Leukaemic cells depend on a higher level of iron uptake to enhance their replication and meet the demands of their active metabolism. A resultant decreased population of erythroid progenitor cells exacerbates the production of healthy red blood cells. Leukaemic cells also cause disruption of iron recycling and imbalance in the entire iron homeostasis in the body. Gaining insights into the ways iron metabolism is deranged in leukemic cells is essential for creating treatment regimens for simultaneously resolving both anemia and the underlying problem in leukemia.

Iron deficiency anaemia is a global health problem caused by a lack of iron inside the body, leading to low red blood cell production. Symptoms usually include anaemia due to low haemoglobin production and exhaustion caused by a deficiency of iron. A shortage of iron may lead to both anaemia and a sensation of fatigue or weakness. This indicates the probability of serious complications like gastrointestinal blood loss (Abdelmahdi et al., 2020; Saxena & Sharma,, 2021). Its occurrence may be linked to an iron deficient diet, decreased absorption or increased loss of iron.

CONCLUSION

Leukaemia perturbs iron metabolism, leading to both the expansion of leukemic cells and an increased risk of iron insufficiency coexisting with the disorder. Cancerous leukemic cells promote the accumulation of iron within individual cells by enhancing the expression and activation of iron import proteins at the same time as they suppress the levels of those responsible for exporting iron from cells. Increased intracellular iron levels enhance leukemia progression, prolong survival and make treatment less effective due to their influences on cellular metabolism, DNA synthesis and oxidative processes. Leukemia leads to anaemia by removing iron from the bone marrow and preventing it from being used to produce healthy red blood cells. This research has revealed how the tumour microenvironment influences how leukemic cells metabolize iron and causes both their own continued growth as well as disrupted hematopoiesis. Making the anemia worse, raised concentrations of inflammatory cytokines inhibit red blood cell production in people with leukaemia. Disturbances in energy metabolism contribute to the problem by requiring more iron and causing changes in the pathways cells use for making and using energy. The study provides a clearer understanding of leukaemia and suggests new possibilities for its

treatment in the future. Bringing together strategies that target iron transport proteins and metabolic manipulation to control leukaemia offers a new way to simultaneously tackle the disease itself and the severe anaemia that frequently results. These new methods are now being investigated as possible treatments in people with leukaemia. The application of these strategies promises to revolutionise leukaemia treatment by providing effective treatments with precision aimed at cancerous cells and few adverse effects. Blending metabolism and iron research may help create customised treatments that dramatically improve the quality of life for individuals with leukaemia.

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