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The Influence of Genetic and Environmental Factors on the Occurrence and Development of Blood Diseases

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Abstract: Hematopoietic disease is due to the abnormal function of the hematopoietic system, is a disease caused by the dual role of heredity and environment. Genetic factors such as gene mutation, chromosome abnormality, immune gene mutation, as well as environmental factors such as exposure to harmful chemicals, viral infection, and living habits are all risk factors for causing blood diseases. Certain gene mutations, such as TP53, JAK2, NPM1, etc., are high-risk for the occurrence of blood diseases, and long-term exposure to harmful chemicals, EBV virus infection, etc., can also lead to the occurrence of blood diseases. This article reviews the influence of genetic and environmental factors on the occurrence and development of blood diseases, and discusses the prevention and control strategies such as early screening, targeted therapy, cell therapy and personalized rehabilitation.

Keywords: blood diseases; gene mutation; environmental exposure

1. Introduction

Blood diseases refer to diseases that are toxic to hematopoietic cells or stem cells due to various reasons, such as acute leukemia, bone marrow proliferative diseases, anemia, lymphoma, etc. The formation and occurrence of these diseases are the result of both genetic and environmental factors, such as gene mutation, chromosome recombination, immune system instability will affect the development of hematopoietic cells and stem cells; Exposure to chemicals (such as benzene or heavy metals), viral infections (such as EBV or HTLV-1), and unhealthy lifestyle habits (such as smoking) can increase the incidence and progression of blood diseases. With the development of medicine, the diagnosis and treatment of blood diseases have entered the era of individuation. Through genetic testing, the mutation status of high-risk groups can be detected, so as to intervene early in the occurrence of diseases. The development of targeted therapy, cell therapy and immune cells will bring the best solution for patients with blood diseases [1].

2. Basic Concepts of Blood Diseases: The Intersection of Heredity and Environment

2.1. Hierarchical Regulation of the Hematopoietic System: Bidirectional Effects of Genes and Microenvironment

Hematopoietic stem cells (HSCs) and their microenvironment constitute the hematopoietic system. The hematopoietic system is influenced by the interaction between gene regulation and microenvironment. Hematopoietic stem cells in the bone marrow environment can be affected by cytokines such as stem cell factor (SCF), leukemia inhibitor (IL-3),

granulocyte colony stimulating factor (GM-CSF), and regulated by related pathways such as JAX-STAT, Notch, Wnt, etc., to maintain the properties of regeneration, development, and differentiation. From the perspective of genes, RUNX1, GATA2 and TP53 genes play a key role in the differentiation of hematopoietic stem cells, and their genetic abnormalities can lead to poor differentiation of the hematopoietic system and lead to blood diseases [2]. The microenvironment consists of bone marrow stromal cells, endothelial cells and macrophages, which can directly interact and secrete or release soluble substances, regulating the hematopoietic system in a state of balance, but external environmental factors (such as benzene, ionizing radiation, viral infection, etc.) can break the microenvironment structure, resulting in DNA damage or chromosomal abnormalities, affecting the proliferation and developmental potential of hematopoietic stem cells. Mathematical models can describe the dynamic changes of hematopoietic cells, such as the growth of hematopoietic stem cells can be expressed as:

$$\frac{dN}{dt} = rN(1 - \frac{N}{K}) \quad (1)$$

Where, N is the number of hematopoietic stem cells, r is the growth rate, and K is the maximum support capacity provided by the microenvironment. The complementary interaction between the microenvironment and genes determines the balance between normal and abnormal hematopoietic system, which ultimately leads to the risk of blood diseases.

2.2. Modern Classification System of Blood Diseases

Due to the development of molecular biology and genomics, the classification of blood diseases is constantly improved, which mainly includes morphology, cytogenetics and molecular biology. Previously, according to the morphological characteristics of blood cells, it could be divided into acute, chronic leukemia, MDS, aplastic disorder, lymphoma, etc. Cytogenetic classification identifies disease types with specific chromosomal variation (such as BCR-ABL fusion -- CML) based on chromosome analysis. Currently, a series of gene mutations related to blood diseases (such as JAK2, NPM1, FLT3-ITD, etc.) have been found using large-scale high-throughput sequencing and other genomic means. Molecular typing becomes an important means of accurate diagnosis of blood diseases. For example, the NPM1 mutation of AML has a relatively good prognosis, but the FLT3-ITD mutation has a poor prognosis. Immunophenotypic classification (such as CD19, CD20, CD34, etc.) can further subdivide blood diseases and improve the targeting of treatment programs [3].

Table 1 shows the different classifications of blood diseases, including morphological classification, cytogenetic classification, molecular biology classification and immunophenotypic classification. Each classification is based on specific biological characteristics, such as morphological classification focusing on cell morphology, cytogenetic classification based on chromosomal abnormalities, molecular classification involving key gene mutations, and immunophenotypic classification dependent on the expression of markers on the cell surface. For example, in chronic myelogenous leukemia (CML), BCR-ABL translocations (t(9; 22)) is a typical genetic marker and responds well to tyrosine kinase inhibitor (TKI) therapy. The table helps to understand the molecular mechanism of blood diseases and its influence on prognosis.

Table 1. Modern classification system of blood diseases.

Classification mode	Main category	Key feature	Representative mutation	prognosis
Morphological classification	AML	Primordial myelocytosis	NPM1、FLT3	The prognosis varies by mutation

Cytogenetic classification	CML	BCR-ABL translocation	t(9;22)	Good. TKI is working
Molecular biological classification	MPN	JAK2 mutation	JAK2 V617F	Chronic progression
Immunophenotype classification	B-ALL	CD19 positive	PAX5、IKZF1	Prognosis depends on genetic changes

2.3. Interaction Mechanism between Heredity and Environment of Blood Diseases

The formation of blood disorders is the result of multiple factors, genetic factors determine whether there is a predisposition to the disease, and there may be causative environmental factors, which cause genetic mutations, or worsening of the disease. Previous data have shown that BRCA1, TP53, ATM and other genetic susceptibility genes participate in the regulatory process of DNA repair and cell cycle regulation, and once these genes are mutated, hematopoietic stem cells will be susceptible to external carcinogenic factors. In addition, EBV and other viral infections also have the process of blood degeneration, which can regulate cell signaling pathways by integrating host genome [4].

Table 2 shows how different genetic mutations interact with environmental factors to influence the development and progression of blood disorders. For example, TP53 mutations are more common in leukemia patients, and when individuals are exposed to benzene, an environmental carcinogen, for a long time, it may further aggravate DNA damage repair disorders and increase the risk of leukemia. Similarly, the JAK2 V617F mutation is associated with myoproliferative disease, and exposure to radiation may exacerbate abnormal proliferation of blood stem cells. In addition, PAX5 mutations are common in patients with B-ALL (acute lymphoblastic leukemia), and EBV (Epstein-Barr virus) infection may affect the development of B cells, thereby inducing leukemia.

Table 2. Interaction model of genetic and environmental factors.

Genetic factor	Related blood disorders	Environmental factor	Influence mechanism
TP53 mutation	Myeloproliferative disease	Benzene exposure	DNA damage repair disorder
JAK2 V617F	Environmental factor	Radiation	Promotes abnormal proliferation of hematopoietic stem cells
PAX5 mutation	B-ALL	EBV infection	Affects B cell development

3. Influence of Genetic and Environmental Factors on Blood Diseases

3.1. Gene Mutation and Genetic Susceptibility

Genetic mutations affect the development of blood disorders, and certain genetic mutations can lead to an increased likelihood of developing certain blood disorders. Hematopoietic stem cells (HSCs) are basic blood components that can achieve normal development and expansion only when a series of important genes are accurately regulated. However, gene mutations may break the balance of the blood system and lead to the occurrence of blood diseases. Mutations such as TP53, JAK2, NPM1, BCR-ABL, RUNX1, etc., are likely to be the main cause of leukemia, myelodysplastic syndrome (MDS), or myelodysplastic diseases (MPNs). For example, JAK2V617F mutation leads to abnormal activation of JAK-STAT signaling pathway, which promotes excessive proliferation of red blood cells and platelets and induces myeloproliferative diseases. When BCR-ABL is translocated (i.e., t(9; 22)), will produce a continuously active tyrosine kinase, this kinase can

stimulate the endless proliferation of leukemia cells, resulting in chronic myeloid leukemia (CML). In addition, TP53 mutations affect the regulation of the cell cycle and the function of DNA repair, leading to a higher risk of blood diseases. The accumulation of genetic mutations can be expressed by the following formula:

$$P_{mutation} = \lambda \times G_{risk} \times t \quad (2)$$

Where, $P_{mutation}$ represents the probability of mutation occurrence, λ is the mutation rate, G_{risk} represents the genetic susceptibility coefficient of the individual, and t represents the time. In recent years, the development of gene sequencing technology has provided a new direction for early screening and risk prediction, enabling precision medicine to be applied in the prevention and control of blood diseases [5].

3.2. Destruction of Hematopoietic System by Environmental Factors

Environmental factors are important exogenous irritants that cause blood diseases. Because the human body is sensitive to harmful stimuli such as various toxic chemicals, radiation, and the spread of pathogens, bone marrow is easily damaged and pathological changes occur. Studies have shown that benzene, heavy metals (such as lead and arsenic), radiation and viral infections (such as EBV virus and HTLV-1) are possible pathologic factors inducing hematopathy. Benzene as a chemical that can induce leukemia, when it is ingested by the human body, it is metabolized in the body to form benzoquinone and DNA damage and chromosome breakage, resulting in hematopoietic stem cell mutations. In addition, radioactive contacts (such as nuclear workers) can cause double-stranded DNA molecules to break due to radiation (high-energy radiation), and cells can't repair properly leading to cancer progression; Viral infections (EBV viruses) may increase the risk of lymphoma and leukemia by interfering with cellular immunity and gene expression in hematopoietic cells.

Figure 1 shows the relative contribution of different environmental factors to the risk of developing blood diseases. According to the data, exposure to benzene, a solvent widely used in the chemical and printing industries that promotes leukemia by inducing DNA damage and chromosomal aberrations, was the leading environmental risk factor, accounting for 40%. Radiation accounts for 25%, and long-term exposure to ionizing radiation (such as X-rays, radioactive substances) can cause mutations in hematopoietic stem cells and increase the incidence of acute leukemia. Viral infections (such as EBV, HTLV-1) account for 20% and can induce blood diseases by affecting the immune system and B-cell differentiation. Heavy metals (such as lead and arsenic) make up 15% of the population and increase the risk of blood diseases by interfering with the DNA repair system and hematopoietic function.

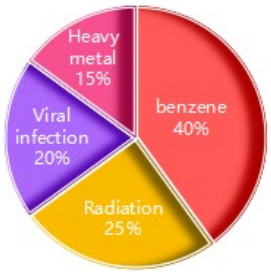

Figure 1. The proportion of major environmental factors affecting blood diseases.

3.3. Synergistic Effect of Genetic and Environmental Factors

There is a complementary relationship between genetic and environmental factors in the occurrence of blood diseases. Studies have shown that individuals with a genetic predisposition are at much higher risk of developing the disease if they are exposed to environmental stimuli, such as chemical or pathogen infections. People with mutations in the TP53 or BRCA1 genes, for example, who are exposed to benzene pollution have blood

cells that are less able to repair DNA, resulting in more mutations. A comprehensive model of blood disease risk can be expressed as follows:

$$P(\text{hemopathy}) = f(G) + g(E) + h(G,E) \quad (3)$$

Where, $f(G)$ represents the contribution of genetic factors, $g(E)$ represents the influence of environmental factors, and $h(G,E)$ represents the synergistic effect of the two. If an individual carries the JAK2 V617F mutation and is exposed to radiation for a long time, the risk of blood disease is much higher than that of the general population.

4. Prevention and Control Strategies of Blood Diseases

4.1. Early Screening and Individualized Prevention

Early screening and individualized prevention of blood diseases are important links to reduce the risk of disease and improve the survival rate. Most of the causes of blood diseases are genetic predisposition and external factors, so early screening strategies such as genetic testing, environmental risk assessment and biomarker detection should be carried out. At present, through precisely targeted gene sequencing technology (NGS), it is possible to find risk genes that are easy to cause diseases, such as TP53, JAK2, NPM1 and RUNX1, and find people who may develop diseases in advance. The use of flow cytometry (FACS) to detect abnormal cell expression in blood can detect early changes in the hematopoietic system. Taking the JAK2V617F variant as an example, its presence in MPNs patient samples has a high specificity, and its application can not only evaluate the prognosis of the disease, but also allow for early therapeutic intervention. In terms of environmental risk factors, risk factors such as benzene, heavy metal pollutants, radiation and viral infections significantly increase the risk of disease, so individualized prevention programs should include occupational protection in the workplace (reducing toxic exposure), good lifestyle habits (smoking cessation, balanced diet) and standardized medical examinations. It is now known that the combination of heritage susceptibility and environmental exposure can increase the risk of blood diseases by 5 to 10 times.

Figure 2 shows the application proportion of different early screening methods in the prevention and control of blood diseases. From the data point of view, genetic testing accounts for 40%, is currently the most important screening means, through high-throughput sequencing (NGS) can identify high-risk gene mutations (such as JAK2, TP53, BCR-ABL), so as to predict the individual risk of disease and early intervention. Environmental risk assessments account for 30% and are used to monitor the effects of external environmental factors such as benzene, heavy metals, radiation and viral infections on the hematopoietic system so that preventive measures can be taken. Biomarker testing also accounts for 30%, mainly by analyzing abnormal proteins, cytokines or mutated DNA in the blood (such as flow cytometry (FACS), peripheral blood ctDNA analysis) to detect early signs of blood diseases.

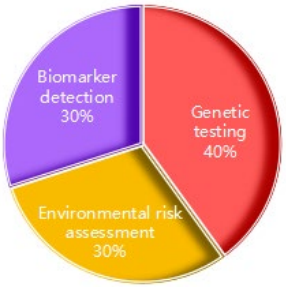

Figure 2. Application ratio of early screening method in prevention and control of blood diseases.

4.2. Targeted Therapy and Cell Therapy

With the development of precision medicine technology, targeted therapies and cell therapies that block the reduction in the regeneration rate of hematologic malignant cells

caused by abnormal activation of signal transduction pathways have become the main treatment methods for hematologic tumors. For example, tyrosine kinase inhibitors (TKIs) used in chronic myelogenous leukemia (CML), that is, Imatinib that targets the abnormal signal of BCR-ABL fusion protein, can significantly inhibit the activation of BCR-ABL fusion protein, thus effectively delaying the progression of leukemia. The JAK2 inhibitor (Ruxolitinib) has also been shown to be an effective treatment for myeloproliferative diseases. In addition, therapies such as CAR-T cell therapy, in which a patient's own T cells are genetically modified to produce receptors that recognize specific markers such as CD19-CAR, also offer a promising new approach to blood cancer treatment. So that it can be targeted to B-cell leukemia and lymphatic cancer attack.

Table 3 shows the application of different types of targeted therapy and cell therapy in blood diseases. TKIs (tyrosine kinase inhibitors) are mainly used to treat chronic myelogenous leukemia (CML), in which Imatinib can effectively inhibit the BCR-ABL fusion gene, enabling more than 90% of patients to achieve long-term remission. JAK2 inhibitors, such as Ruxolitinib, are indicated for myeloproliferative disorders (MPNs) to reduce JAK-STAT signaling pathway activity, reduce abnormal hemocytosis, and reduce the risk of thrombosis. In addition, CAR T cell therapy genetically engineered CD19-CAR T cells to kill B-cell leukemia and lymphoma cells, and its complete remission rate can reach 80%, becoming an important breakthrough in the treatment of blood tumors.

Table 3. Comparison of targeted therapy and cell therapy.

Treatment mode	Target point	indication	Representative drugs/technologies	Curative effect
TKIs	BCR-ABL	CML	Imatinib	More than 90% of patients have long-term remission
JAK2 inhibitor	JAK2	MPNs	Ruxolitinib	Improves symptoms and reduces the risk of blood clots
CAR T cell therapy	CD19	B-ALL, B-cell lymphoma	CD19-CAR-T	The complete remission rate was 80%

4.3. Comprehensive Management and Personalized Rehabilitation

Treatment options for patients with blood disorders include drug therapy and cell therapy, and require long-term multi-disciplinary collaboration and individualized rehabilitation planning. Because the treatment cycle is relatively long, patients must be systematically integrated with multiple professional areas (such as hematology, oncology, rehabilitation medicine, nutrition and cardiology) that operate simultaneously. Treatment mainly includes the following aspects: core treatment: immune system monitoring, nutrition optimization, exercise intervention, psychological counseling. For patients undergoing bone marrow transplants, for example, maintaining long-term testing is necessary to prevent complications and also to help reduce risk. Personalized rehabilitation programs for leukemia patients also include increased demand for vitamin B12, folic acid and iron, which are essential for promoting blood production, and appropriate exercise programs (such as yoga and tai chi) to increase blood circulation and immune system functioning. The comprehensive effect of rehabilitation management can be calculated by the following formula:

$$Q_{recovery} = \frac{I_{nutrition} + P_{psychology} + R_{exercise}}{T_{treatment}} \quad (4)$$

Among them, $Q_{recovery}$ represents the quality of rehabilitation, $I_{nutrition}$ is the nutrition intervention index, $P_{psychology}$ is the psychological support index, $R_{exercise}$ is the sports rehabilitation index, $T_{treatment}$ represents the treatment time.

5. Conclusion

The occurrence and development of blood diseases are the products of genetic and environmental factors. Genetic mutations (e.g., TP53, JAK2, BCR-ABL) may affect blood production, while environmental factors (e.g., benzene exposure, radiation, infection with viruses) may cause and promote such mutations, increasing an individual's risk of developing disease. In addition, the interaction of genetic and environmental factors also makes the pathogenic factors of hematological malignant diseases more complicated. In terms of prevention, personalized diagnosis and treatment of early screening and early diagnosis, especially targeted therapy and cell therapy, have achieved considerable results. Genetic screening identifies vulnerable people and improves cure rates with targeted drugs and CAR-T cell therapy. Personalized rehabilitation and comprehensive management are the key to improve patients' quality of life.

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