

The Role of Genetic Mutations in Genes RUNX1, RUNX1T1, CBFβ & MYH11 on Core Binding Factor Acute Myeloid Leukemia

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1. Abstract

Acute myeloid leukemia (CBF-AML) is one of the causes of hematopoietic tissue (bone marrow) called acute myeloid leukemia. In normal bone marrow, early blood cells called hematopoietic stem cells develop into several types of blood cells: white blood cells (leukocytes) that protect the body against infection, red blood cells (erythrocytes) that carry oxygen and platelets (thrombocytes) play a role in blood coagulation, in acute myeloid leukemia, the bone marrow produces a large number of abnormal and immature white blood cells called myeloid blasts. Instead of turning into normal white blood cells, myeloid blasts turn into cancerous blood cells.

2. Overview of Binding Factor Acute Myeloid Leukemia (CBF-AML)

Acute myeloid leukemia (CBF-AML) is one of the causes of hematopoietic tissue (bone marrow) called acute myeloid leukemia. In normal bone marrow, early blood cells called hematopoietic stem cells develop into several types of blood cells: white blood cells (leukocytes) that protect the body against infection, red blood cells (erythrocytes) that carry oxygen and platelets (thrombocytes) play a role in blood coagulation, in acute myeloid leukemia, the bone marrow produces a large number of abnormal and imma-

ture white blood cells called myeloid blasts. Instead of turning into normal white blood cells, myeloid blasts turn into cancerous blood cells. A large number of abnormal cells in the bone marrow interferes with the production of functional white blood cells, red blood cells, and platelets [1].

3. Clinical Signs and Symptoms of Factor-Binding Acute Myeloid Leukemia (CBF-AML)

People with CBF-AML have a lack of mature blood cells: a lack of white blood cells (leukopenia) leads to increased susceptibility to infections, a low number of red blood cells (anemia) causes fatigue and weakness and loss of appetite. A low platelet count (thrombocytopenia) can lead to easy bruising and abnormal bleeding. Other symptoms of CBF-AML may include fever and weight loss [1].

While acute myeloid leukemia is generally a disease of older adults, CBF-AML often begins in young adulthood and can occur in childhood. Compared to other types of acute myeloid leukemia, CBF-AML has a relatively good prognosis: about 90 percent of people with CBF-AML recover from their disease after treatment, compared with 25 to 40 percent of people with other forms of acute myeloid leukemia. Others are acute myeloid leukemia. However, the disease recurs in about half of them after successful treatment of the initial occurrence [1] (Figure 1).

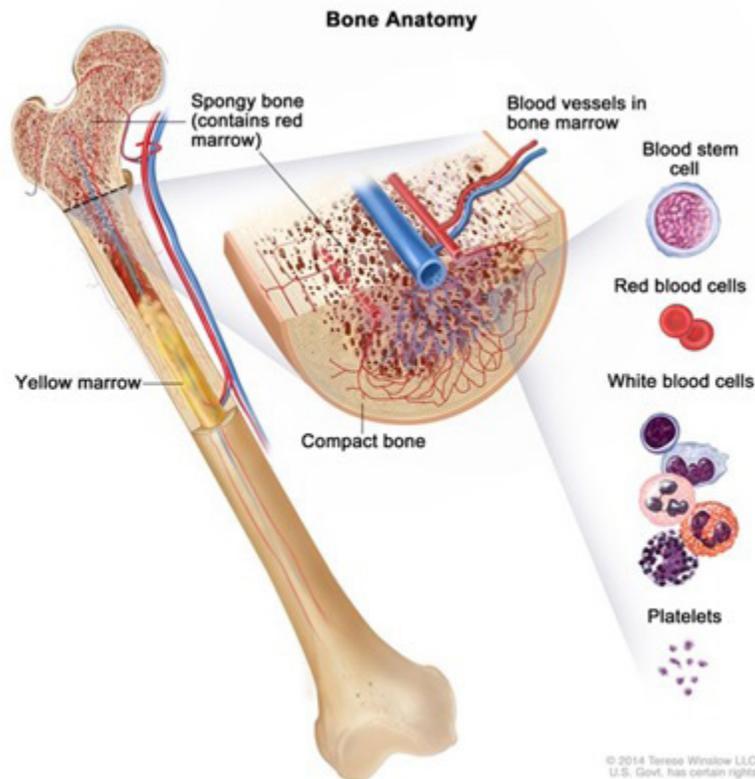


Figure 1: Schematic of bone anatomy [1].

4. Etiology of Acute Myeloid Leukemia Binding Factor (CBF-AML)

CBF-AML is associated with chromosomal rearrangements between chromosome 8 and chromosome 21 and within chromosome 16. The rearrangements include RUNX1, RUNX1T1, CBFβ and MYH11 genes. Two of these genes, RUNX1 and CBFβ, provide the instructions for making two pieces of a protein complex known as binding factor (CBF). CBF binds to specific regions of DNA and turns on genes that help control the development of blood cells (hematopoiesis). In particular, it plays an important role in the development of hematopoietic stem cells. Chromosomal rearrangements involving the RUNX1 or CBFβ gene alter CBF and lead to leukemia. In CBF-AML, the RUNX1 gene is affected by a type of genetic rearrangement called a translocation. In this type of change, DNA fragments from two chromosomes are broken and moved with each other. The most common translocation in this condition is called (21;8)t, which combines part of the RUNX1 gene on chromosome 21 with part of the RUNX1T1 gene (also known as ETO) on chromosome 8. The combination of these genes leads to the production of RUNX1-ETO fusion protein. This fusion protein is able to form CBF and bind to DNA like normal RUNX1 protein. However, because the function of the protein produced from the normal RUNX1T1 gene is to block gene activity, abnormal CBF turns genes off rather than turning them on [1,2].

Other genetic rearrangements associated with CBF-AML change the CBFβ gene. One such rearrangement, called an inversion, involves breaking the chromosome in two places. The obtained

DNA fragment is reversed and re-enters the chromosome. The CBF-AML inversion (written as (16)inv) results in the fusion of two genes on chromosome 16, CBFβ and MYH11. Rarely, a translocation involving chromosome 16, written as (16;16)t, results in the fusion of two identical genes. The protein produced from this genetic rearrangement is called CBFβ-MYH11. The fusion protein can form CBF, but the presence of the MYH11 portion of the fusion protein is thought to prevent CBF from binding to DNA and impair its ability to control gene activity. Alternatively, the MYH11 segment may interact with other proteins that prevent the control of CBF gene activity [1,3].

The change in gene activity caused by the change in CBF blocks the maturation (differentiation) of blood cells and leads to the production of abnormal myeloid blasts. However, a chromosomal rearrangement alone is usually not sufficient to cause leukemia. One or more additional genetic changes are required to cause cancer. Additional changes likely cause uncontrolled growth and division of immature cells, leading to the overgrowth of myeloid blasts characteristic of CBF-AML. CBF-AML is not inherited, but results from genetic adjustments in the body's cells that occur after conception [1,4].

5. Frequency of Binding Factor Acute Myeloid Leukemia (CBF-AML)

Acute myeloid leukemia occurs in approximately 3.5 of 100,000 people each year. CBF-AML accounts for approximately 12% to 15% of acute myeloid leukemia cases in adults [1,5].

6. Diagnosis of Acute Myeloid Leukemia Binding Factor (CBF-AML)

Acute myeloid leukemia binding factor (CBF-AML) can be diagnosed based on the clinical and clinical findings of patients and some pathological tests. The most accurate method of diagnosing this disease is molecular genetics and molecular cytogenetics in order to check the presence of possible mutations [1,6].

7. Treatment Pathways for Acute Myeloid Leukemia Binding Factor (CBF-AML)

The treatment and management strategy of CBF-AML is symptomatic and supportive. There is no effective treatment for this disease and all clinical measures are aimed at alleviating the suffering of the sufferers. Genetic counseling is also necessary for all parents who want a healthy child [1,7].

8. Conclusion

People with CBF-AML have a lack of mature blood cells: a lack of white blood cells (leukopenia) leads to increased susceptibility to infections, a low number of red blood cells (anemia) causes fatigue and weakness and loss of appetite. A low platelet count (thrombocytopenia) can lead to easy bruising and abnormal bleeding. Other symptoms of CBF-AML may include fever and weight loss. The rearrangements include RUNX1, RUNX1T1, CBF and MYH11 genes. Two of these genes, RUNX1 and CBF, provide the instructions for making two pieces of a protein complex known as binding factor (CBF). CBF binds to specific regions of DNA and turns on genes that help control the development of blood cells (hematopoiesis). In particular, it plays an important role in the development of hematopoietic stem cells. Chromosomal rearrangements involving the RUNX1 or CBF gene alter CBF and lead to leukemia. The treatment and management strategy of CBF-AML is symptomatic and supportive. There is no effective treatment for this disease and all clinical measures are aimed at alleviating the suffering of the sufferers [1-7].

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