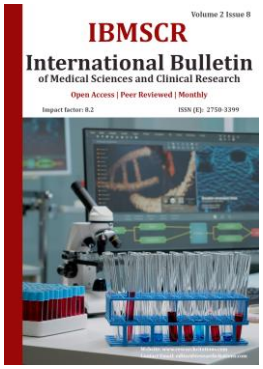

THE ROLE OF INTRACELLULAR SIGNALS IN THE BONE MARROW IN THE PATHOGENESIS OF CHRONIC MYELOID LEUKEMIA

Bobonazarova M.N.
3rd year student of Tashkent Medical Academy, treatment faculty
Sharofiddinova Z.Sh.
3rd year student of Tashkent Medical Academy, treatment faculty
Matkarimova D.S.
professor of department of hematology and clinical laboratory, Tashkent Medical Academy
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Abstract: Until today, one of the most dangerous diseases in the field of medicine is leukemia, the etiology and pathogenesis of which has not been fully determined. According to world statistics, leukemia is 13.2% per 100,000 population. Chronic myeloid leukemia, which ranks 3rd among common blood diseases, accounts for 15-20% of all leukemias.

The main role in the pathogenesis of hemoblastosis is focused on the gene system, where the importance of gene biotransformation, xenobiotics, and the role of modifiers of the main genes has been proven. Accordingly, one of the tasks of modern oncohematology is to determine the role of gene variation in the pathogenesis and clinic of hemoblastosis and to develop measures aimed at its prevention and treatment. In the bone marrow of a healthy person, mature blood cells are selectively passed through the wall of sinusoidal capillaries. In chronic myeloid leukemia, which is a type of leukemias, there is an increase in the permeability of the capillary wall, and this process is explained by the importance of special receptors, adhesion molecules and chemoattractants in the capillaries in the release of hemopoietic cells into the blood.

Key words: chronic myeloid leukemia, sinusoidal capillaries, Philadelphia chromosome, imatinib, mobilization of hematopoietic cells

Introduction: Chronic myelogenous leukemia (CML), also known as chronic myeloid leukemia, is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells. CML accounts for 20% of all leukemias affecting adults. Most of the causes of leukemia are still unclear. In modern medicine, there are several factors that lead to the development of CML: radiation, oncogenic virus strains, chemical factors, genetic predisposition, endogenous deficiencies (hormonal, immune), etc. Currently, the mutational theory occupies the most important place in the mechanism of development of leukemia. Due to mutated genes in the DNA of blood-forming cells, immature young blast cells enter the bloodstream without differentiation. The occurrence of this mutation is related to the fact that the ABL gene on the 9th chromosome of the genome joins the BCR gene on the 22nd chromosome, and as a result of translocation, the BCR-ABL fusion gene is formed. The altered chromosome 22 is called the Philadelphia chromosome with the fusion gene. The ABL gene is usually the gene that synthesizes the protein tyrosine kinase. The abnormal tyrosine kinase synthesized from the translocated BCR-ABL gene causes proliferation and uncontrolled division of hematopoietic cells. Imatinib which is one of the most common used drug to treat chronic myeloid leukemia works by inhibiting an abnormal tyrosine kinase produced by the

Philadelphia chromosome. Imatinib and other drugs of its second generation have a selective effect on abnormal tyrosine kinases, but 20-30% of patients have not positive results. According to scientists, the reason for such results is a violation of the selective permeability of the sinusoidal capillaries in the bone marrow in chronic myeloid leukemia.

Main part: There is such a process in the pathogenesis of chronic myeloid leukemias, which can be the basis for making certain clarifications in their etiology, clinic, diagnosis and treatment. This is the process by which mature blood cells are released into the veins. The process of creation and release of blood cells in the human body takes place in the bone marrow. Maturity, differentiation and release of hematopoietic stem cells in the bone marrow are based on several mechanisms, and the wall of the sinusoid capillaries in the bone marrow plays an important role in these processes. In both normal and pathological cases, hematopoietic cells leave the bone marrow through sinusoidal capillaries. Several substances in the capillary wall, including CAM (cell adhesion molecules), chemoattractants, and receptors are important in the mobilization of mature or stem cells into the blood. Below we will consider some of them.

Chemokines and microenvironment of leukemia stem cells. First of all, we will consider the role of cell adhesion molecules (CAM) in the capillary wall in the release of hematopoietic cells. Studies have shown that constitutively expression of cell adhesion molecules such as P-selectin, E-selectin and VCAM-1 by bone marrow sinusoidal capillaries is necessary for hematopoietic stem cells to move towards the capillaries. Some of these adhesion molecules are predicted to be important for specific subtypes of hematopoietic cells. For example, normal hematopoietic cells bind to VCAM-1 on endothelium, whereas CD34+ cells bind to ICAM-1, ICAM-2, and ICAM-3 adhesions (the CD34 transmembrane glycoprotein serves as a marker of stem and progenitor cells).

In addition, some receptors are also involved in the mobilization of mature and blast hemopoietic cells. Scientists have determined the mutually exclusive distribution of ephrin B4 (EPHB4) receptors in bone marrow sinusoids and ephrin B2 (EPHB2) ligands in hematopoietic cells. A signaling interaction between EPHB4 and EPHB2 was found to control mobilization of the hematopoietic lineage cells from the bone marrow. Blockade of the EPHB4/EPHB2 signaling pathway in mice reduced the mobilization of stem cells and other myeloid cells into the circulation. In addition to inhibiting cell migration, EphB4 knockdown restored sensitivity to the abnormal tyrosine kinase inhibitor drugs that are mentioned above.

The mechanism of migration of stem cells in the bone marrow is also provided by the signals emitted by chemoattractants in these spaces. Migration of stem cells from osteoblastic niches to vascular niches is controlled by many signals, including c-kit/Stem Cell Factor (SCF); CXC depends on chemokine receptor 4 (CXCR4)/stromal-cell derived factor-1 (SDF-1) and granulocyte colony-stimulating factor (GCSF). For example, CXCL12, a chemokine, participates in the mobilization of stem cells and hematopoietic progenitor cells together with its receptor CXCR4, which is expressed by stem cells and Rac family molecules.

G-CSF- (granulocyte colony stimulatory factor) stimulates the bone marrow to produce mature granulocytes and release them into the bloodstream. G-CSF also stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils through signal transduction pathways. Direct administration of G-CSF into the bone marrow vasculature induced selective mobilization of neutrophils by reducing the

expression of CXCR4 in the bone marrow and CXCL12 in neutrophils, suggesting that disruption of CXCL12/CXCR4 signaling by G-CSF was shows that it is an important switch in the release of stimulated neutrophils. That's why currently drugs such as lenograstim and filgrastim containing G-CSF are widely used in the practice of oncohematology.

Conclusion: In order to find a solution to leukemia, which is one of the most important problems in world medicine, it is necessary to consider its etiology and pathogenesis at the cellular and molecular level. As one of the major obstacles in the current treatment of leukemia is the excessive egress of leukemic cells from the bone marrow and invasion into various tissues/organs, it is important to investigate the potential role of bone marrow sinusoidal endothelial cells in the egress of leukemic cells and pathological changes that appear in this disease.

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